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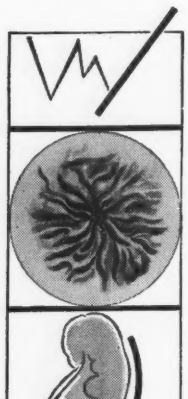

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Volume 246 JUNE 5, 1952 Number 23

THE ANTIBIOTIC THERAPY OF TUBERCULOUS MENINGITIS*

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DURING the five-year period 1947–1951, 40 cases of tuberculous meningitis in children were treated with antibiotics at the North Reading State Sanatorium. This institution has been designated as a treatment center for children with active lung tuberculosis. The majority of the meningitis patients came from hospitals throughout the state after diagnosis was made and treatment started in those hospitals.

The observation periods have been long enough, in a considerable number of the cases, to enable the writers to formulate some concepts concerning the management of the most serious form of tuberculosis. A variety of the therapeutic regimens employing para-aminosalicylic acid (PAS) and Promizole as additive agents to streptomycin were put into effect. Attempt was therefore made to assess the value of PAS and Promizole as additive agents.

Progressive improvement in the therapy of tuberculous meningitis tends to improve the case fatality rate spectacularly. This is especially true in children. This fact has introduced the troublesome problem of serious neurologic disability in many survivors. Our aim is to focus attention on this situation. We believe that further elucidation of the problem and a search for rational methods of remedying the situation are, at the present time, the most important objectives of those interested in the cure of this form of tuberculosis.

Comments on the Literature

The literature on tuberculous meningitis is voluminous. The earlier literature contains numerous case reports or series so small with observation periods so short as to render them unsuitable as bases of comparison with our cases. It was therefore considered impractical to review the entire literature. Some papers are, however, considered briefly.

In March, 1950, the Streptomycin Committee of the Veterans Administration filed its report on the status of chemotherapy in human tuberculosis to the American Medical Association Council on Pharmacy and Chemistry.[1] The report is based on 7000 cases, with all forms of tuberculosis, in which 22 different streptomycin regimens were employed. This committee studied the results of streptomycin therapy in 100 cases of miliary and meningeal tuberculosis. These were reported in detail by Bunn.[2,3] The second of two reports by this author deals with a two-year follow-up study of the 100 cases. Eighty-one patients had meningitis with or without miliary tuberculosis. Ten of these survived and 71 succumbed. It is important to note that these were all adults and that it is now known [2,4,5] that the prognosis is much worse in adults than in children over the age of two. Bunn used 1.8 gm. of streptomycin intramuscularly for 100 to 185 days and 50 to 100 mg. of streptomycin intrathecally for 45 injections. He reports a high incidence of fatal relapse and a large number of survivors with serious neurologic disorders.

Shamaskin and his co-workers[6] reported on 30 adult patients with miliary and meningeal tuberculosis. Of the 17 with meningitis only 4 survived. These authors state that "none of the patients developed meningitis if no symptoms were exhibited during the first 2 months of streptomycin in miliary tuberculosis." The latter assertion is extremely important from the standpoint of prevention.

In February, 1950, Lincoln and Kirmse[7] reported on the Promizole-streptomycin treatment of tuberculous meningitis in children. The treatment consisted of streptomycin, 1 gm. daily intramuscularly for 180 days; intrathecal streptomycin in doses of 50 to 100 mg. for a series of 40 injections and Promizole orally in doses of 1 to 8 gm. daily in divided doses. The Promizole was given uninterruptedly for three years. Sixteen out of a total of 21 patients survived. A high percentage of the survivors had some form of neurologic disability, varying in degree from mild to severe.

Illingworth and Lorber[8] reported on 82 cases of tuberculous meningitis in children treated with streptomycin. Thirty-eight had miliary tuberculosis concomitantly with the meningitis. They used

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TABLE 1. *Cases of Tuberculous Meningitis Treated With Antibiotics.*

CASE No.	SEX	AGE	CEREBROSPINAL FLUID BEFORE TREATMENT						TREATMENT		
			DURATION OF MENINGITIS BEFORE THERAPY	CELLS	PROTEIN	SUGAR	TUBERCLE BACILLI RECOVERED	TUBERCULOUS FOCI IN LUNGS	DATE THERAPY STARTED	SCHEDULE	NO. OF COURSES
		yr.	*days*								
1	M	1 1/12	7	106			Yes	Miliary	6/2/47	A	¼
2	F	1	10	340	150	Absent	Yes	Primary active	4/7/48	A	2
3	M	2	22	612	167	Absent	Yes	Primary active	12/20/47	A	4
4	M	1	20	93	110	Decreased	No	Miliary	10/13/47	A	⅛
5	F	2	22	187	126	Decreased	No	Miliary	6/2/48	A	2
6	M	3	21	800	68	Decreased	Yes	Miliary	3/24/49	B	2
7	F	2½	21	310	121	50	Yes	Miliary	2/8/50	B	5
8	F	1	7	60	32	10	Yes	Primary inactive	5/30/49	M	2
9	M	9	14	159	100	25	Yes	Pulmonary far advanced	10/27/49	C	1½
10	F	2	14	241	46	Decreased	Yes	None	11/27/48	B	9
11	M	5/12	21	18	130	Decreased	No	Miliary	6/30/48	M	
12	M	4/12	30	331	100	30	No	Miliary	7/1/49	C	8
13	F	3	6	188	234	Absent	Yes	None	11/23/48	C	7
14	M	1½	12	520	2400	Absent	No	Miliary	10/11/48	B	8
15	M	3	21	400		Absent	No	Miliary	8/24/49	C	4
16	M	6	9	462	136	25	No	Primary active	8/11/49	B	4
17	M	3½	14	200	81	Absent	Yes	Primary inactive	7/1/49	C	5
18	F	7	10	170	61	25	Yes	Primary active	9/2/49	B	5
19	F	5	14	73	100	25	No	None	3/13/50	B	8
20	F	12	23	247	174	25	Yes	Primary inactive	12/28/48	B	8
21	F	5½	6	84	54	30	Yes	Miliary	7/13/50	C	6
22	F	6	1	180	100	Decreased	No	Miliary	5/17/50	B	4
23	M	4½	4	550	110	Decreased	Yes	None	7/28/50	B	9
24	M	8½	10	12	20		Yes	Miliary	4/20/50	C	7
25	F	2	15	143	110	21	No	Primary inactive	1/24/51	B	5
26	M	2½	15	880	135	Decreased	No	Primary active	5/4/49	C	6
27	M	2/12	7	174	100	15	Yes	Primary active	7/19/49	B	6
28	F	1½	7	180	190	Decreased	No report	Miliary	7/4/50	C	3
29	F	3½	2	249	75	35	Yes	Miliary	7/12/51	B	On therapy
30	F	6	5	540	130	Decreased	Yes	None	8/19/51	B	On therapy
31	F	15	14	538	124	30	No	None	4/25/51	B	On therapy
32	M	15	20	690	200	62	No	None	11/26/50	C	On therapy
33	M	10½	7	178	2617	60	No	Primary inactive	7/13/51	B	On therapy
34	M	1½	7	300	96	Decreased	Yes	Primary inactive	3/1/51	B	On therapy
35	F	1	8	102	67	54	Yes	Primary inactive	6/10/50	C	On therapy
36	M	6	9	380	80	53	No	None	5/5/51	B	On therapy
37	M	1	15	20	193	32	Yes	Primary active	5/24/47	M	
38	F	2½	21	21	199	30	Yes	None	1/15/51	B	4
39	M	10	14	180	121	67	Yes	None	9/5/51	M	On therapy
40	F	5	7	400	222	Absent	Yes	None	10/22/51	B	

TABLE 1 (*Concluded*).

CASE NO.	TREATMENT				MOST RECENT CEREBROSPINAL FLUID IN SURVIVORS				REMARKS
	DATE THERAPY COMPLETED	PERIOD OF OBSERVATION SINCE START OF THERAPY	PERIOD OF OBSERVATION SINCE END OF THERAPY	RESULT	CELLS	PROTEIN	SUGAR	TUBERCLE BACILLI RECOVERED	
		mo.	*mo.*						
1				Died					X-ray evidence of miliary tuberculosis 6 wk. before meningitis; no PAS; spinal block.
2				Died					
3				Died					Active disease in lungs
4				Died					20 days with meningitis before therapy; 20-mg. doses intrathecally, no PAS.
5				Died					Ill 22 days before therapy; no PAS.
6				Died					Ill 21 days before therapy; had miliary tuberculosis.
7				Died					Spinal block; relapse.
8				Died					
9				Died					Pulmonary tuberculosis far advanced over 3 mo.; no streptomycin.
10				Died					Block; relapse; hydrocephalus.
11	1/24/49	42	33	Disabled	1	20	50	No	Markedly retarded; left hemiplegia; blind.
12	3/9/50	29	15	Disabled	8	40	45	No	Retarded; moderate paresis left lower extremity.
13	5/15/50	37	19	Well	4	30	40	No	Excellent condition
14	4/11/50	38	20	Disabled	8	100	50	No	Retarded, moderately
15	1/4/50	28	24	Disabled	2	30	40	No	Deaf; asphasic; markedly retarded.
16	4/3/50	28	20	Well	4	20	40	No	Excellent condition
17	3/10/50	29	21	Disabled	2	25	40	No	Deafness; moderately retarded.
18	5/4/51	27	8	Disabled	3	30	40	No	Hemiparesis, left—improving
19	5/26/51	21	7	Disabled	2	35	35	No	Markedly retarded; aphasia; left hemiplegia.
20	4/28/51	24	7	Well	4	50	40	No	Mild unilateral deafness; otherwise excellent.
21	4/17/51	17	7	Well	2	10	40	No	Above average intelligence
22	11/2/50	18	13	Well	3	25	45	No	Excellent to date
23	10/25/51	17	2	Well	3	40	40	No	Excellent result to date
24	10/17/51	20	2	Disabled	3	40	35	No	Marked deafness (? bilateral)
25	8/20/51	11	4	Disabled	4	15	35	No	Spastic monoplegia
26	3/10/50	31	21	Well	4	30	40	No	Disabled by pre-existent tuberculosis of spine
27	4/20/51	28	7	Well	4	15	35	No	Recovered from meningitis; still has primary active tuberculosis.
28	4/13/51	17	8	Disabled	4	20	40	No	Block; deaf; blind; retarded; relapsed; critical.
29		5		Well	25	50	30	No	Excellent; still on treatment.
30		4		Well	8	15	40	No	Excellent; still on treatment.
31		7		Well	5	50	40	No	Excellent; still on treatment.
32		13		Well	17	75	35	No	Excellent; still on treatment.
33		5		Disabled	40	15	35	No	Block; still on treatment.
34		9		Disabled	21	75	40	No	Moderately retarded; still on treatment.
35		18		Disabled	12	20	35	No	Markedly retarded; still on treatment.
36		7		Well	16	20	35	No	Appears well to date; still on treatment.
37	6/4/47	54	54	Disabled	0	100	35	No	Marked retardation; hydrocephalus; blind; deaf; block.
38	7/16/51	11	6	Disabled	5	20	35	No	Marked retardation; deafness; blindness.
39		3		Disabled	134	100	30	No	Marked retardation; right hemiplegia.
40		3		Well	55	53	35	No	—

streptomycin intramuscularly in doses of 20 mg. per pound of body weight for six months and streptomycin intrathecally in doses of 25 to 75 mg. for twenty-one days followed by a rest period of seven days and 21 more daily doses — a course of treatment consisting of 42 intrathecal injections. If the spinal-fluid and clinical findings were not near to normal, another course was given. Of the total of 82, 46 died and 36 survived. These cases are considered important, as a large number had been observed for a relatively long time.

Russell and MacArthur[9] reported on 33 cases of meningitis in children treated with streptomycin. They were among the first to report that streptomycin is irritating to the meninges and causes thickening of the leptomeninges. They noticed the latter condition in a patient dying twenty-two days after treatment was begun. They were among the first to observe that streptomycin given intramuscularly appears in the cerebrospinal fluid in small quantity if the meninges are normal but in larger quantities if the meninges are infected. They suggest that prolonged intrathecal therapy may be harmful. Five patients were treated with intramuscularly administered streptomycin only; all died. Of the 33 patients, 18 died, 10 are alive and well and 5 are alive and disabled. Seven relapsed; of those, 3 died, 2 are seriously disabled and 2 are well. These authors conclude that the prognosis is relatively good in children if treatment is early, if the patient is at least two years old or more and if there is no evidence of active disease in the lungs.

MacCarthy and Mann[10] reported on 43 cases of tuberculous meningitis in children treated with streptomycin. Twenty-nine died and 14 survived. They also reported very poor results in cases treated only with streptomycin administered intramuscularly. Six patients receiving such therapy died. They recommend a three-month course of combined intramuscular and intrathecal therapy with no less than 50 intrathecal injections, followed by intramuscular administration of streptomycin until the cerebrospinal fluid has been normal on two tests over a period of three months.

Hinshaw and his group[11] have been working on the subcutaneous administration of the sodium salt of para-aminosalicylic acid. Their results thus far seem to show high promise for PAS as a suitable additive agent in the therapy of meningitis. They find that the spinal-fluid level is relatively high when the drug is administered subcutaneously. As is well known, PAS given orally cannot be recovered from the spinal fluid in any appreciable quantity.

Several papers were selected because they serve to explain the high incidence of neurologic disorders in the streptomycin-treated survivors. Significant on the subject are the reports of Winter,[12] Auerbach[4, 5] and the Veterans Administration Streptomycin Committee.[1] Comments on these papers will appear under "Discussion."

Treatment

Four schedules of treatment were employed. They are shown in Table 1 as A, B, C and M (miscellaneous) — A: streptomycin intramuscularly and intrathecally; B: streptomycin intramuscularly and intrathecally with PAS orally; C: streptomycin intramuscularly and intrathecally with PAS and Promizole orally; and M, all other forms of therapy.

The dose for streptomycin intramuscularly was 100 mg. per kg. of body weight (never in excess of 1.5 gm. daily). The dose for intrathecal administration was, except in a few cases, 50 mg. The dose for PAS was 0.2 gm. per kg. of body weight in divided doses. The dose for Promizole varied between 1 and 6 gm. daily in divided doses, depending on tolerance. A course of therapy consisted of 4 daily injections intrathecally, followed by an injection on alternate days for a period of six weeks. The latter was accompanied by daily intramuscular injections of streptomycin in the dosage mentioned. PAS, when used, was given orally daily in divided doses from the beginning of treatment and for six months after cessation of streptomycin treatment. Promizole administration was the same as that of PAS. After the conclusion of the six-week course the patient was given a ten-day "rest period," during which intramuscular and intrathecal administration of streptomycin was omitted. Promizole and PAS were continued uninterruptedly in the manner outlined.

Table 1 (under "Treatment") lists the number of courses given to patients who have completed treatment (20). The minimum number of courses used was 3, the maximum 9. A six-week course consisted of 23 intrathecal injections and 42 intramuscular injections. Streptomycin was stopped when the spinal fluid stabilized with a cell count of 0 to 12 and a protein of 10 to 40, as well as a negative culture over a period of about two months.

Some writers doubt the value of the "rest periods." We are continuing to use the rest period because it frequently helps us to determine whether a sudden increase in spinal-fluid cells is due to streptomycin *per se*. This was found to be especially valuable in Case 24 (Table 1). During his seventh course of treatment this patient suddenly developed a marked increase in cells. After cessation of streptomycin, the cell count fell to normal and has remained normal to date. Tucker's report[13] on the various regimens employed by the Veterans Administration suggests that the interruption of therapy at regular intervals tends to delay the emergence of resistant organisms. It is difficult to ascertain whether the rest periods aid in accomplishing this desirable effect in cases of meningitis.

Schedule A was employed in 5 cases; B in 20 cases; C in 11; and M (miscellaneous) in 4 cases. Of the

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latter group, 1 patient (Case 8) received streptomycin intramuscularly and intrathecally with oral Promizole but no PAS. Case 11 received streptomycin intramuscularly with PAS and Promizole orally but no intrathecal therapy. Case 37 received streptomycin intrathecally in a single dose of 2 gm. (at another hospital). The child has marked hydrocephalus, total bilateral blindness, bilateral deafness and marked mental deterioration. It is of interest that his spinal fluid, which before the injection was positive on culture, has remained negative on culture to date (a period of about four years). Case 39 received no intrathecal treatment during the first two months of illness. At present, he is on Schedule B. He developed a left hemiplegia early in his disease, as well as rather marked retardation. There is progressive but slow improvement since the institution of Schedule B.

Results

Table 1 lists the cases and the results obtained. We prefer to list the duration of the meningitis (in days) rather than to name the stage of the disease, as certain other writers have done.[7, 8, 10] Naming the stage of the disease is at best subjective and may frequently be inaccurate.

Tubercle bacilli were recovered in 24 out of the 40 cases, negative cultures were obtained in 15 and no report has been received in 1 case. In the cases with negative cultures the diagnosis was relatively certain on the basis of other findings in the spinal fluid, the presence of tuberculosis elsewhere, positive skin tests, positive cultures of gastric contents and response to specific therapy.

To summarize the results of therapy: Of the 40 patients, 10 (25 per cent) died and 30 (75 per cent) survived. Fourteen of the survivors remain well (46.7 per cent of survivors) and 16 remain disabled (53.3 per cent of survivors).

For purposes of comparison of survival rates, we have listed 6 other series of cases in Table 6. It may be seen that the survival rate in the cases here reported was the second highest. This is partly because 2 of the 5 series were predominantly adult groups and, as was previously mentioned, the outlook for survival is poorer in adults than in children. We believe that Promizole probably had little or no influence on the outcome but that PAS may be of definite value, especially in the cases associated with active lung disease. It remains to be seen what effect the subcutaneous administration of the sodium salt of PAS will have in future cases of meningitis.

Deaths

At this time it is well to mention briefly the factors that probably contributed to a greater or lesser extent to the 10 cases ending in death. Seven of the 10 patients were two years old or less. Eight had active disease in the lungs. Of the latter group 5 had miliary tuberculosis, 2 a very active form of primary progressive disease and 1 an extensive, active reinfection type of tuberculosis of the lung. Five of the patients developing active lung disease prior to meningitis received no specific treatment until streptomycin was given when meningitis was diagnosed. In 8 of the deaths, meningeal signs had been present for fourteen days or longer prior to institution of treatment. Additive agents were omitted in 5 of the fatal cases. In 1 case no intrathecal therapy was ever given.

Disabilities

One of the most disturbing facts about this disease is the high incidence of neurologic and neuropsychiatric disabilities. We were somewhat surprised, therefore, to note in surveying the literature that this important problem has not been given the emphasis it deserves.

It must be stressed that 16 of the 30 survivors were disabled. The disabilities varied in degree from minor to very severe.

The commonest type of disability was a variable degree of mental retardation. This occurred in 11 of the 16 disabled patients. In 3 of the cases (28, 34 and 37) retardation was associated with hydrocephalus. The second most common type of disability, with or without retardation, was some form of motor disturbance in one or more extremities. This occurred in 8 cases. There were 8 cases of deafness (2 unilateral and 6 bilateral). There were 4 cases of blindness of varying degree and bilateral blindness in 3 of the 4. There were 2 cases of serious speech disorder.

Three patients relapsed. Two died during the relapse; 1 is alive but in very poor condition. Two of the 3 who relapsed, did so, we believe, because therapy was stopped after only 2 courses of treatment. As was stated above, we believe that a minimum of 3 courses is required in all cases, regardless of the spinal-fluid findings.

Six patients had block, 3 died, 2 are disabled and 1 is alive and appears in satisfactory condition to date.

Eight of the 16 patients with disability were two years old or less. All writers on the subject agree that the prognosis, both for life and for disability, is much worse in this age group.[4, 5, 7, 8, 10]

The factors that might have contributed to the neurologic disorders noted in 16 of the survivors deserve some mention. Nine of the 16 were under two years of age. Eight had active disease in the lungs. Meningeal symptoms were present for twelve days or longer in 10 cases, for ten days in 2 cases for eight days in 1 and for seven days in the remaining 3. Six patients were on Schedule B, 6 on C and 4 on miscellaneous regimens. Analysis suggests that the same factors (age of patients, duration of illness, coexistence of active disease in lungs and type of therapy) that contribute to fa-

tal termination also contribute to the incidence of disability.

Well Patients

Fourteen of the 30 survivors are considered well. Of that group 6 are still under treatment but have been under observation long enough to justify our belief that they will remain well. Twelve out of the 14 well patients are over the age of two and a half. Seven of the 14 well patients had meningitis for less than a week before treatment was started, 3 less than two weeks and 4 more than two weeks. Six had active disease in the lungs, 2 had primary inactive disease and 6 had no demonstrable tuberculosis in the lungs. Ten received Schedule B; 4 received Schedule C.

Comments on Tables 2, 3, 4 and 5

Table 2 shows a correlation of the results with the schedule of treatment. It is of interest that all

Table 2. *Correlation of Results with Schedule of Treatment.*

Schedule of Treatment	No. of Patients	Well	Disabled	Died
A	5	0	0	5
B	20	10	7	3
C	11	4	6	1
M	4	0	3	1
Totals	40	14	16	10

of the 5 patients who were treated on Schedule A died. Twenty patients received Schedule B (the addition of orally given PAS to intramuscularly and intrathecally administered streptomycin). This group, it is noted, showed the best results. Ten of these 20 patients remain well; 7 were disabled; and

Table 3. *Correlation of Result with Type of Tuberculosis in Lungs.*

Tuberculosis in Lungs	No. of Patients	Well	Disabled	Died
Miliary — meningeal	14	3	6	5
Primary, active	7	3	2	2
Pulmonary far advanced, active	1	0	0	1
Primary, inactive	8	2	5	1
None	10	6	3	1
Totals	40	14	16	10

3 died. The group receiving Schedule C (the oral addition of PAS and Promizole to intramuscularly and intrathecally given streptomycin) included 11 patients. Four remained well; 6 were disabled; and 1 died.

Four patients received miscellaneous forms of therapy; 3 are disabled, and 1 is dead.

Table 3 shows a correlation of the results with the types of tuberculosis in the lungs. Fourteen cases had miliary tuberculosis with their meningitis, 7 had primary active tuberculosis and 1 had far advanced active pulmonary tuberculosis. Of these 22 with active lung disease, it will be noticed that 8 died, 8 were disabled and 6 remain well. Eight patients had primary inactive tuberculosis, and in 10 cases the disease was not demonstrable in the lungs. Of these 18 patients, 8 were well, 8 were disabled and 2 died. It can therefore be seen in Table 3 that the prognosis is much worse in cases of meningitis associated with some form of active tuberculosis in the lung, especially miliary tuberculosis.

Table 4. *Period of Observation Since Beginning of Treatment.*

No. of Months	No. of Patients
48 or over	1
47–36	3
35–24	8
23–12	8
11–6	5
Less than 6	5
	30

Table 4 lists the periods of observation since the beginning of treatment in the 30 survivors. Twenty of the 30 survivors have been observed for periods of one year or longer. Twelve patients have been observed for periods of two years or longer from the beginning of treatment.

Table 5 lists periods of observation since the end of treatment. This includes only the 20 patients who have completed treatment; 10 are still under treatment. Of the group of 20 cases, 10 have been observed for over one year, 7 for six months or over and 3 for less than six months since the end of treatment.

Table 5. *Period of Observation Since End of Treatment.*

No. of Months	No. of Cases
48 or over	1
35–24	2
23–12	7
11–6	7
Less than 6	3
	20

Discussion

Although it is now apparent that the outlook for survival in tuberculous meningitis has improved spectacularly with the use of streptomycin and PAS, there remains the serious problem of an alarmingly high incidence of residual neurologic disorders among the survivors. The report of the Streptomycin Committee of the Veterans Administration[1] sheds some light on this problem. The report includes the following interesting facts: "15% of the 55 surviving patients with meningitis had residual central nervous system stigmas; pathologic studies of the brains of patients who died with tuberculous meningitis disclosed destruction of the basal ganglia in 23 per cent, healing by fibrosis in 45% and some

degree of hydrocephalus in 75%." The problem becomes greater as the survival rate becomes higher. This is demonstrated in our cases, as well as in those of Lincoln and Kirmse.[7] The papers by Winter,[12] Auerbach[4, 5] and Silverthorne and Silverman[14] offer further elucidation of this important problem. Winter studied the pathology in the brain and meninges of 12 patients with meningitis treated with streptomycin for periods varying between twenty-four and 150 days. He noted marked thickening of the pia and arachnoid. Fibrosis, often about foci of caseation, was the commonest and most prominent feature. Many of the vessels underwent stenosis, and areas of ischemic softening could be seen in the brain substance. As in the Veterans Administration cases, the basal ganglia and internal capsule were the commonest sites of softening.

It thus seems that the explanation of the neurologic disturbances is to be found in the nature of the reparative processes attending treatment with streptomycin. However, the fact that some patients remain well even after prolonged periods of streptomycin therapy is encouraging and demonstrates that under certain circumstances the neurologic sequelae may be reduced to a minimum if not eliminated entirely. Such favorable results presumably depend on early diagnosis and adequate intrathecal therapy instituted promptly and continued long enough. It is of interest in this connection that the 2 best results in our series (Cases 21 and 23) were shown after 6 and 9 courses of treatment respectively. The duration of the meningitis prior to treatment was, respectively, six and four days. The fact that these 2 patients had 6 and 9 courses respectively suggests that the length of time during which streptomycin is administered intrathecally is *per se* not an important factor contributing to fibrosis. What is important is the length of time during which there is active exudation and living tubercle bacilli.

It is our opinion that in some cases adequate intrathecal therapy can sterilize the spinal fluid in an exceedingly short period of time. In Case 30, for example, the spinal fluid was sterilized after 3 intrathecal injections of 68 mg. each. The result to date in this case promises to be excellent.

The prognosis for children two years or younger is very poor, even when the diagnosis is made early. In all cases the outlook is complicated if there is coexisting active tuberculosis in the lungs — especially miliary tuberculosis.

The outlook is much better in children than in adults. This is due to the fact that the pathogenesis of the disease is different in children from that in adults, as admirably explained in two reports by Auerbach.[4, 5] Since nearly all the cases have their origin in the primary complex, early and adequate treatment of this condition should prevent meningitis or, if meningeal symptoms have already developed, further feeding of organisms to the central nervous system would be interrupted.

We believe that prevention of the disease in children has not received the attention it deserves. As was previously pointed out, the disease in children has its origin in the primary complex. We now believe that if all patients with primary progressive tuberculosis dating from birth to three years are isolated and treated with streptomycin, tuberculous meningitis might be largely prevented. It is our practice to do monthly spinal-fluid examinations in all children under three years hospitalized with primary active tuberculosis in the lungs; in those with miliary tuberculosis, no matter what their age, spinal-fluid checks are made even more frequently.

Table 6. *Survival Data in Sampled Reports.*

Author	No. of Cases	No. of Survivors	Percentage of Survivors	Additive Drugs
Bunn[3] (excluding miliary without meningitis)	81	10	12.3	None
Shamaskin[6]	17	4	23.5	None
Illingworth and Lorber[8]	82	36	43.9	None
Russell and MacArthur[9]	33	15	45.5	None
MacCarthy and Mann[10]	43	14	32.6	None
Lincoln and Kirmse[7]	21	16	76.2	Promizole
Ravreby et al.	40	30	75	PAS and Promizole

Summary and Conclusions

Forty cases of tuberculous meningitis are reported. Comments on the literature, details of treatment regimens and results are outlined. Suggestions for prevention of fatal or crippling meningitis are mentioned.

The following conclusions appear indicated on the basis of our observations:

Antibiotic therapy has resulted in a markedly better prognosis for tuberculous meningitis in children.

Streptomycin is by far the most important drug used in the treatment of tuberculous meningitis. The drug should be administered both intramuscularly and intrathecally. The minimum intrathecal dose is 50 mg; the minimum number of injections, in our opinion, is about 65.

The addition of PAS increases the survival rate, especially in patients with miliary tuberculosis.

The status of Promizole is as yet undetermined.

The coexistence of active disease in the lungs makes the prognosis worse.

The prognosis is very poor in children two years of age or younger.

The incidence of serious neurologic disorders is alarmingly high, and to date the only remedy is early diagnosis and prompt and adequate treatment.

The authors wish to express their appreciation to Drs. Donald S. King, William Berenberg and Claire W. Twinam for their valuable criticisms and suggestions.

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BREAST-CANCER PROGNOSIS AND OVARIAN CORTICAL STROMAL HYPERPLASIA*

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THE relation between hyperplasia of the stroma of the ovarian cortex and cancer in the human female was first indicated by Smith[1] in his review of endometrial cancer. Subsequently, Woll and his co-workers[2] reported its occurrence in the ovaries of 84 per cent of 331 patients with endometrial cancer. Sommers and Teloh[3] showed an association in cases of carcinoma of the human female breast. At autopsy they found cortical stromal hyperplasia in the ovaries of 83 of 100 women with cancer of the breast, as opposed to an incidence of 37.5 per cent in a control group.

In cases of stromal hyperplasia the ovaries appear grossly to be more nodular and bosselated than when normally atrophied and gyrate. In both cases, the ovaries feel firm and fibrous. On cut section the outer hyperplastic cortical layers form a rather tan-colored homogeneous thickened rind, which in the hematoxylin-and-eosin-stained microscopical section appears unusually dense blue. The blue material frequently extends into the ovarian medulla.

Microscopically, there is an increased amount of cortical stromal whorling and fascicle formation. The nuclei are longer and broader than usual, collagen is very scant and the reticular fibrils are relatively prominent. In some cases these changes are accentuated, and small clear spaces are noted in the ground substance. In a few cases, some of the stromal cells become large and similar to epithelial cells; they have a prominent nucleolus and a distinct cell border and are filled with lipid, so-called "thecomatosis." Thecomatosis may give rise to small granulomatous masses composed of giant cells and lymphocytes and may be associated with the formation of intra- and extracellular crystals of anisotropic fat.[2]

Interest in the possible prognostic significance of these findings was aroused at Pondville Hospital when 2 patients with breast cancer were surgically castrated, had no ovarian cortical stromal hyperplasia and died within one month.

Accordingly, histologic sections of all ovaries removed for castration in breast-cancer cases were reviewed, the reviewers having no knowledge of the patients' clinical courses. The criteria of Woll and others[2] were used to determine the presence or absence of stromal hyperplasia (Fig. 1 and 2). The results were then correlated with the clinical courses, taking into consideration the duration of the disease from onset to death and the time from castration to death.

There were 31 such cases in our file. Three were eliminated because the ovaries were largely replaced by tumor. Of the remaining 28 cases, the ovaries in 20 were hyperplastic and those in 8 were atrophic; 72 per cent had cortical stromal hyperplasia and 28 per cent had none. This is somewhat lower than the incidence of breast cancer reported by Sommers and Teloh in autopsied cases but is well above the incidence in their control group.

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Two other cases, both with ovarian hyperplasia, were eliminated from this group because the patients are still living and well. It was thought that these might represent cures by mastectomy, in which case later castration could have no effect on the prognosis.

The age distribution in both groups was substantially the same (Tables 1 and 2). The average age of the patients with ovarian stromal hyperplasia was forty-one years and the median age 40.5. The average age of those without this condition was forty-four years and the median was the same.

There was considerable difference in survival time of the two groups from onset of cancer to death. The average survival time in the hyperplastic group was forty-one months and the median time was thirty-nine months. The corresponding figures in those with atrophied ovaries were twenty-three and 22.5 months.

Even more pronounced were the differences in the times from castration to death in the two groups. The average post-castration survival time in the group showing stromal hyperplasia of the ovaries was twenty-three months, or 56 per cent of the total average duration of disease. The average duration in the group with atrophied ovaries was 6.5 months, or 28 per cent of the average total duration of the breast cancer. The median post-castration survival times were 15.5 and four months, respectively. These last figures represent 40 per cent of the median total disease duration in those with ovarian hyperplasia and 18 per cent of the median total duration in those with none.

FIGURE 1. *Section of Ovary, Showing Cortical Stromal Hyperplasia, in a Woman Who Lived Ten Months After Castration. The cortex is cellular and abundant and extends deep into the medulla. (Hematoxylin and eosin stain, x34.)*

DISCUSSION

Although statistical significance cannot be established in a series of only 28 cases,* the striking differences observed between disease duration and post-castration longevity indicate a relation between ovarian cortical stromal hyperplasia and the growth activity of breast cancer.

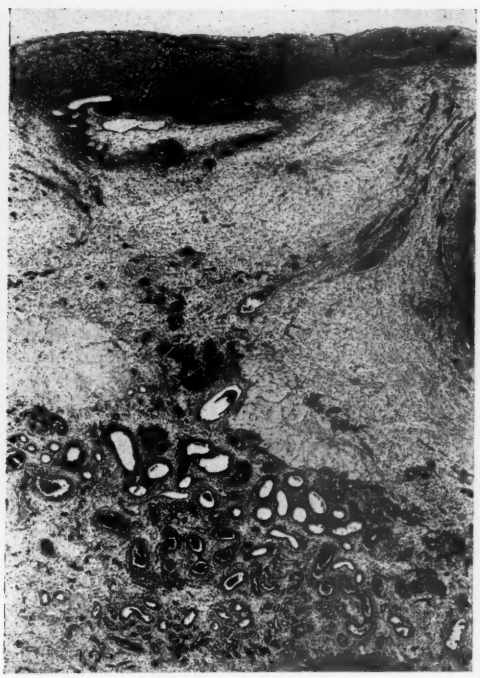

FIGURE 2. *Section of Atrophic Ovary from a Woman Who Died One Month after Castration. The cortex is thin and partly hyalinized, and the medulla is fibrotic. (Hematoxylin and eosin stain, x34.)*

In breast cancer experimentally produced in mice, estrogens are well established as carcinogenic, aside from the hereditary and milk factors involved. Previous studies of human endometrial and breast-cancer series support the belief that ovarian cortical stromal hyperplasia is anatomic evidence of

*Dr. Herbert L. Lombard kindly confirmed the lack of statistical significance in this small group of cases.

excessive ovarian estrogen production. It has been found most frequently at ages near the menopause.

If the thesis be accepted that ovarian cortical stroma produces estrogenic hormones, castration would remove this major endogenous estrogen source. Breast cancers could thus be suspected clinically and pathologically of partial dependence on ovarian hormones for continuing growth and spread. Those patients without ovarian stromal overgrowth have such short post-castration survival times that their ovaries may in contrast have acted to inhibit production of other hormones that stimulate cancer growth. In these cases, the adrenal cortex would appear the most likely source of such growth-enhancing hormones.

Surgical castration has been strongly advocated for inoperable or metastatic breast cancers in premenopausal women. Surgical case selection accounts for the fact that the average age in this series is in the low forties and perhaps explains the somewhat lower percentile incidence of ovarian cortical stromal hyperplasia found as compared with series of unselected autopsied cases.

In the majority of breast cancers in premenopausal women, oöphorectomy has a temporary effect on the tumor that is somewhat comparable with that produced by castration of men with prostatic carcinoma. Both neoplasms appear only incompletely independent of hormonal stimuli. Similar situations of therapeutic importance probably remain to be discovered.

Summary

Microscopical sections of ovaries surgically removed from 31 women with carcinoma of the breast showed an incidence of 72 per cent with ovarian cortical stromal hyperplasia. The total duration of the disease in the women with ovarian cortical stromal hyperplasia was almost twice that of the patients who showed none. Post-castration survival time was shorter in women whose ovaries did not show cortical stromal hyperplasia.

The therapeutic effect of castration for carcinoma of the female breast appears to be poor in the absence of cortical stromal hyperplasia of the ovaries.

Table 1. *Summary of 18 Cases of Breast Cancer with Ovarian Stromal Hyperplasia.*

Case No.	Age	Diagnosis	Mastectomy	Metastases		Duration	
				pre-castration	post-castration	total no. of months	no. of months after castration
	yr.						
1	51	Adenocarcinoma*	Radical	—	Soft tissue	42	30
2	35	Inflammatory carcinoma	None	—	Bone	33	14
3	36	Carcinoma simplex	Radical	—	Bone	39	34
4	46	Carcinoma*	Radical	Bone	—	39	28
5	29	Carcinoma simplex	Radical	—	—	87	73
6	50	Carcinoma simplex	Radical	—	Soft tissue	46	20
7	50	Carcinoma simplex	Radical	—	Bone	70	61
8	30	Carcinoma simplex	Radical	—	Bone, soft tissue	19	15
9	39	Carcinoma simplex	Radical	—	Soft tissue	25	23
10	48	Carcinoma simplex	Radical	—	Bone	54	32
11	43	Carcinoma*	Simple	—	Soft tissue	32	16
12	39	Adenocarcinoma	None	Soft tissue	Bone	29	13
13	42	Adenocarcinoma	Radical	Bone	—	51	11
14	39	Carcinoma*	None	Soft tissue	—	6	1
15	31	Carcinoma simplex	Radical	Bone, soft tissue	—	58	11
16	46	Carcinoma*	Radical	Bone	—	68	10
17	49	Carcinoma*	Radical	Soft tissue	—	25	11
18	42	Inflammatory carcinoma	None	—	Bone	17	4

*Pathological diagnosis made elsewhere.

Table 2. *Summary of 8 Cases of Breast Cancer without Ovarian Stromal Hyperplasia.*

Case No.	Age	Diagnosis	Mastectomy	Metastases		Duration	
				pre-castration	post-castration	total no. of months	no. of months after castration
	yr.						
1	38	Carcinoma simplex	None	—	—	3	1
2	42	Carcinoma simplex	Radical	—	—	15	8
3	50	Carcinoma simplex	Radical	Bone	—	38	4
4	39	Carcinoma simplex	Radical	Bone	—	25	4
5	46	Carcinoma simplex	Radical	Soft tissue	—	42	19
6	54	Inflammatory carcinoma	None	Soft tissue	—	20	14
7	46	Carcinoma simplex	Radical	Soft tissue	—	28	1
8	34	Carcinoma simplex	None	Soft tissue	—	14	1

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PERIODIC NEUTROPENIA TREATED BY ADRENOCORTICOTROPHIC HORMONE AND SPLENECTOMY*

Report of a Case

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DETROIT, MICHIGAN

NEUTROPENIA associated with oral ulcers, periodic fever, benign paroxysmal peritonitis and intermittent arthralgia has been observed to occur with cyclic regularity. In 1949 Reimann and de Berardinis[1] reviewed 16 cases from the literature, including one of their own, and concluded that there were grounds for establishing an entity that they designated as a "periodic neutropenia." In the same year, Fullerton and Duguid[2] reported a similar case, which they followed for 500 days through 12 attacks of illness characterized by malaise, anorexia, drowsiness, headache, pyrexia and inflammation of the throat and tongue, with painful superficial ulcers of the oral mucosa. They demonstrated that each attack of clinical illness was preceded by complete disappearance of neutrophilic granulocytes from the peripheral blood and that when the neutrophils reappeared the patient's clinical illness rapidly improved.

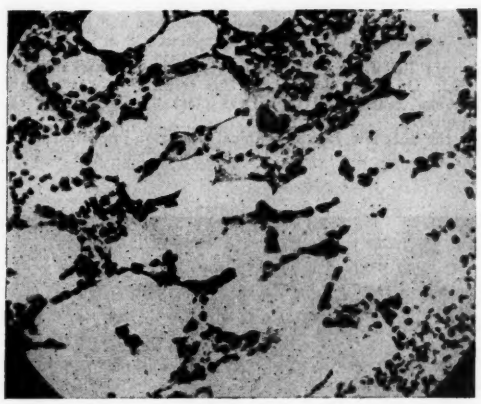

FIGURE 1. *Section of Aspirated Marrow Particles: Stage of Clinical Relapse (Hemotoxylin and Eosin, x300).*

The following case (Fig. 1) seems to fulfill the criteria of "Periodic Neutropenia."

CASE REPORT

H. C. W., a 78-year-old man, was initially seen by a dentist in 1949, complaining of recurring attacks of "canker sores" of 1 year's duration. He presented two large aphthae on the mucous membrane of the lower lip and on the tip of the tongue. There was no cervical-node enlargement or scarring of the mouth. These lesions were treated by various measures, including local cautery, but continued to recur in "crops" at intervals of about 3 weeks. Each attack was accompanied by mild fever. In April, 1950, his three remaining teeth were extracted. Two days later he developed chills and a temperature of 102.6°F. The fever persisted in spite of penicillin and chloramphenicol administration, and he was admitted to the Henry Ford Hospital.

The patient had been in remarkably good health most of his life. As a child he contracted diphtheria and had repeated attacks of quinsy. His family history was entirely negative for blood dyscrasias; both his parents had lived to old age. From 1942 to 1949 he had contact with paints and varnish in his occupation, when he worked as a maintenance man in a factory that manufactured these products. He did not handle these substances directly but did repair machines used in their manufacture.

Physical examination revealed a well developed and well nourished elderly man who was febrile but not severely ill.

TABLE 1. *White-Cell Studies in a Case of Periodic Neutropenia.*

DATE	WHITE BLOOD CELLS	NEUTROPHILIC GRANULOCYTES	METAMYELOCYTES	LYMPHOCYTES	MONOCYTES
		%	%	%	%
4/17/50	700	2	1	60	31
4/19/50	1,050	19	7	60	13
4/20/50	1,250	30	10	41	19
4/21/50	1,600	44	8	35	13
4/22/50	1,800	49	6	38	7
4/23/50	2,500				
4/24/50	1,900				
4/27/50	2,800				
4/28/50	3,900	53		47	
5/ 7/50	3,950	36		64	
5/20/50	1,500	11		89	
5/28/50	1,550	13		80	7
6/12/50	1,800	37		54	7
7/ 8/50	650	3	1	92	4
7/10/50	600				
7/11/50	500	ADRENOCORTICOTROPHIC HORMONE STARTED			
7/12/50	600				
7/13/50	700				
7/14/50	1,650	67		24	9
7/15/50	1,700				
7/16/50	2,400				
7/17/50	1,400	55		41	2
7/18/50	2,750				
7/19/50	3,100				
7/20/50	2,900	65		26	8
7/21/50	3,600				
7/22/50	3,650				
7/23/50	3,200				
7/24/50		SPLENECTOMY			
7/25/50	16,450	91		8	1
7/27/50	6,400	88		12	0
7/29/50	4,700				
7/31/50	5,300				
8/10/50	2,450	2		79	7
8/29/50	4,450	31		60	9
9/19/50	6,900	22		75	3
9/27/50	6,900	27			
10/24/50	6,350	25			
1/16/51	5,800	8	4	79	6
6/26/51	5,000	0		94	6
7/19/51	4,050				
8/ 4/51		0		97	3
8/15/51	3,050	7		79	14

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He showed slight pallor, and his breath was foul. The tongue appeared pink without ulcerations. There were small raised areas on the gums, giving a pebbled appearance. The craters of the recently extracted teeth appeared to be healing. The remainder of the general examination was not unusual for a man of his stated age.

Urinalysis, blood-sugar and nonprotein-nitrogen determinations and Kline exclusion test for syphilis were normal. The blood count showed a hemoglobin of 12.6 gm., a red-cell count of 4,290,000 and a white-cell count of 700, with 2 per cent neutrophilic granulocytes, 61 per cent lymphocytes and 31 per cent monocytes. Blood cultures were sterile for pathogenic organisms. Agglutinations for *Salmonella typhosus, S. paratyphosus B* and *Brucella abortus* were negative. A chest x-ray film was normal. Smears of the throat demonstrated the usual mixed mouth flora and were negative for *C. diphtheriae*. The patient was treated with penicillin and chloramphenicol. Serial white-cell counts and differentials are shown in Table 1. Six days after hospitalization the temperature was normal and the patient appeared much improved. His clinical condition and white-cell levels remained satisfactory for approximately 3 weeks, when he again developed fever and a new ulcer in the mouth.

The first bone-marrow study was performed in June, 1950, at a time when the patient was relatively free of signs and symptoms of his disease. This showed a myeloid-erythroid ratio of 0.89 to 1. There was marked depression of cells of the granulocytic series, but the granulocytes showed a normal differential spread. There was relative increase in the erythroid cells and many megakaryocytes were present (Table 2).

On July 5, 1950, ulceration of the mouth and tongue recurred, and on the following day he developed fever and diarrhea. Two days later his temperature rose to 105°F., and he complained of soreness in the rectum. The patient was readmitted to the hospital on July 7, 1950. Physical examination revealed an acutely ill and delirious patient with obvious evidence of weight loss. An anal ulcer was found, but the remainder of the physical examination was unchanged. The hemoglobin was 10.4 gm., the red-cell count 3,120,000 and the white-cell count 650. The differential showed 1 per cent metamyelocytes, 3 per cent neutrophilic granulocytes, 92 per cent lymphocytes and 4 per cent monocytes. Red cells and platelets appeared normal on the blood smear. The urine showed + albumin and few granular casts. Blood cultures were sterile. The nonprotein nitrogen was 36 mg., and the blood sugar was 123 mg. per 100 cc. The reticulocyte count was 0.2 per cent, the blood sodium 308 mg., the chlorides 500 mg. and the potassium 13 mg. per 100 cc. A second bone-marrow aspiration gave a myeloid-erythroid ratio of 2.1 to 1. Hypocellularity and marked granulocytic depression were present (Table 2 and Fig. 1).

Despite administration of streptomycin and penicillin and fresh blood transfusions, the patient's condition continued to deteriorate. His temperature fluctuated from 101°F. to 105°F. The total white-cell count remained between 500 and 600, with almost complete absence of neutrophilic granulocytes (Table 1). On July 10, 1950, his respirations were 42 per minute, coarse rales were present throughout both lung fields and his condition was considered critical. That evening (3 days after admission) he was started on ACTH 20 mg. every 4 hours. After the second injection his temperature fell from 102°F. to 98°F., and he appeared remarkably improved. On the following day his respiration was normal, the lungs cleared and there was marked regression of the anal ulcer.

In the next few days his clinical condition improved markedly, and the diarrhea ceased. The patient was afebrile, alert and rational and ate well. The dosage of ACTH was gradually reduced and was discontinued after 8 days. A progress bone-marrow aspiration on this date revealed a myeloid-erythroid ratio of 4.9 to 1. The marrow was remarkably

TABLE 2. *Sternal Bone-Marrow Aspirations.*

CELLS	NORMAL PERCENTAGE	JUNE 2, 1950	JULY 10, 1950	JULY 17, 1950	JANUARY 16, 1951
No. of cells counted		500	400	500	500
		%	%	%	%
Reticulum cells	Occasional	1.0	1.5	0.4	0.2
Myeloblasts	1		2.0	0.2	0.4
Progranulocytes	2	1.2	19.0	0.8	1.8
Neutrophilic myelocytes, early	4	3.4	0	3.0	1.4
Neutrophilic myelocytes, late	13	7.6	0	21.2	1.8
Neutrophilic metamyelocytes	15	2.8	0.3	10.0	1.6
Band cells	16	17.2	0.5	32.2	4.8
Neutrophils, segmented	15	6.4	2.87	10.2	7.6
Eosinophilic myelocytes, early	2	0.2			0.2
Eosinophilic myelocytes, late	2	0.2			0.2
Eosinophils	1				0.4
Tissue mast cells	Occasional		0.5		0.2
Lymphocytes	10	5.0	38.6	3.4	32.4
Monocytes	1	0.4	0	0	6.2
Plasmacytes	1	0.8	1.0	0.2	1.2
Megakaryocytes	—	Many	Many	Moderate	
Pronormoblasts	0.5	1.4	0.5	0.6	0.6
Basophilic normoblasts	2	3.0	2.0	0.6	0.8
Polychromic normoblasts	12	48.4	29.0	16.0	37.6
Orthochromic normoblasts	4	0	0	0.4	0.8
Phagocytic histiocytes	Occasional		2.0		
Mitoses, white	—	0.2	0.3	0.4	
Mitoses, red	—	0.6	0	0.4	0.2

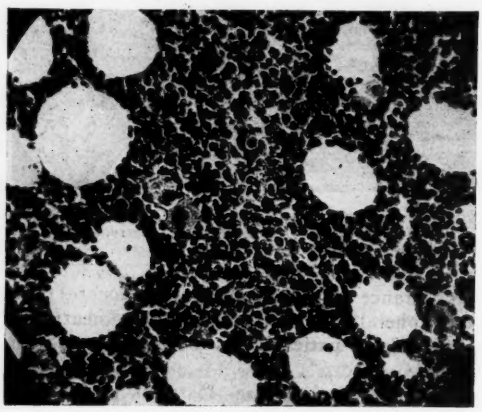

FIGURE 2. *Section of Aspirated Marrow Particles Seven Days After Figure 1: Stage of Clinical Remission after ACTH Therapy (Hematoxylin and Eosin, x300).*

hyperplastic, in marked contrast to the marrow study made before ACTH therapy (Fig. 2). There were many more than the normal number of cells; the increase in marrow cellularity was particularly notable in the absolute and relative increase in the granulocyte series.

The patient's total blood-cell count remained at a level of 3000 to 4000 cells, with an increase of neutrophilic granulocytes to 65 per cent. His clinical condition appeared good. In an effort to prevent a recurrence of severe periodic crises, palliative splenectomy was elected. On July 25, 1950, a moderately enlarged spleen weighing 520 gm. was removed without incident. It was grossly normal in appearance; microscopical examination of the tissue revealed a normal capsule, with a slight increase in fibrous tissue throughout the splenic pulp. The Malpighian corpuscles were normal except for a moderate degree of sclerosis of the central vessels. The red pulp showed numerous prominent, empty sinusoidal spaces, the endothelium of which showed hypertrophied cells.

On the first postoperative day the white-cell count increased to 16,450, with 91 per cent neutrophils and 8 per cent lymphocytes. The white-cell count remained at a level of 5000 cells throughout the remainder of his hospital stay. He was discharged from the hospital on August 1, 1950, in apparently excellent condition.

Six days later the patient again developed fever rising to 103°F. The physical examination was negative. The white-cell count was 1700. Aureomycin was given orally. In 3 days the temperature returned to normal. Soreness of the rectum developed, and endoscopic examination revealed a large ulcer of the anus. At this time the white-cell count was 2450, with 2 per cent neutrophilic granulocytes, 79 per cent lymphocytes and 7 per cent monocytes. The anal ulcer healed slowly.

The patient was followed in the outpatient department at monthly intervals. His white-cell count varied from 4000 to 7000, with 8 per cent to 2 per cent neutrophilic granulocytes. He has had two episodes of mild ulceration of the mouth, one in September, 1950, and one in December, 1950. In January, 1951, his blood count was: hemoglobin 15.6 gm., platelets 186,000, white cells 5800, neutrophilic granulocytes 8 per cent, lymphocytes 79 per cent, monocytes 6 per cent and metamyelocytes 4 per cent. His reticulocyte count was 1.6 per cent. His bone marrow at that time showed a myeloid-erythroid ratio of 1.5 to 1 and the cellularity was described as "at the lower limits of normal" (Table 2).

Discussion

Periodic neutropenia has been described most often in infancy, 9 of 16 patients reported being under two years of age. The sixty-two-year-old man reported by Fullerton is the oldest previously recorded case.

The interval between episodes of neutropenia in the observed cases has ranged from fourteen to twenty-eight days and has usually been twenty-one days. The intervals varied in this case from seventeen to twenty-five days. The cyclic nature of the disease has suggested an endocrinologic mechanism, but correlation of the granulocyte level and sex-hormone excretion has not been established.[1, 3-5] Other attempts to discover etiologic factors in this disease have also failed.[2] The seven-year exposure to paint and varnish cannot be minimized as an etiologic factor in this patient, even though he had no contact with these chemicals for a year prior to our observation.

The changes that occurred in the patient's condition after the administration of ACTH were dramatic. Prior to this therapy the patient was delirious, the temperature was 105°F. and the respiratory rate was 42 per minute. Within sixteen hours the temperature was normal, respiratory distress was absent and the patient was oriented. The total white-cell counts had remained at a level of 600 to 700 prior to ACTH, but seventy-two hours after initiation of therapy the count increased to 1650 cells, with 67 per cent neutrophilic granulocytes. A progress bone-marrow examination made six days after ACTH therapy revealed a hyperplastic marrow with a marked increase in the number of cells of the granulocytic series (Fig. 2). In view of the gravity of the patient's pretreatment status, the sudden improvement in the clinical and hematologic condition of the patient was attributed to a therapeutic response rather than the "recovery phase" of a cyclic episode. It is to be noted that the protracted

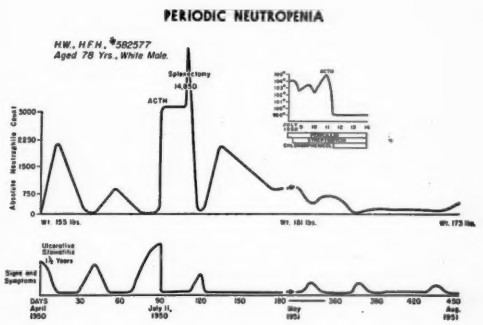

Figure 3.

hypocellular and quantitatively immature bone-marrow picture prior to treatment reverted to a markedly hyperplastic marrow with cellular maturity six days after therapy. The alteration of the bone-marrow picture was more abrupt with ACTH than in the serial studies of Fullerton's patient throughout a cycle of the disease. Reimann was able to demonstrate a sharp rise in the number of neutrophilic granulocytes after a single 25-mg. injection of ACTH in his case. In view of these observations, it is reasonable to regard ACTH as a part of the preparation of such patients for splenectomy.

Splenectomy has been performed in 6 cases, with improvement in 4. The patient of Reznikoff was reported as clinically improved, but there was no significant alteration of the hematologic condition after splenectomy. Fullerton and Duguid's patient was only symptomatically improved. Similarly, the cases of Doan[6] and Erf[7] received benefit from splenectomy. After the removal of the spleen in our patient, the white-cell count rose to 16,450, with 91 per cent neutrophilic granulocytes. Within a few days the count fell to 6400, with 88 per cent neutrophils. In the sixteen months since operation the total white-cell count has not been observed

below 2450, with most determinations ranging between 4000 and 6000.

Although there have been episodes of neutropenia with mild infections of the mucous membranes, severe system infections have not occurred, and the patient has gained 26 pounds in weight and has required no further hospitalization. The possible compensatory defensive function of the lymphocytes observed in the patient's peripheral blood is considered worthy of note.

Conclusion

A case of chronic granulopenia in a seventy-eight-year-old man is presented.

The clinical and hemotologic course showed "cyclic" fluctuations suggestive of periodic granulopenia.

Marked clinical improvement and favorable changes in blood and bone marrow occurred after the administration of ACTH.

Symptomatic improvement of a year's duration was effected by splenectomy.

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MEDICAL PROGRESS

ACQUIRED FISTULA BETWEEN THE ESOPHAGUS AND THE RESPIRATORY TRACT*

Report of a Case, Review of the Literature and Discussion of the Pathogenesis

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BALTIMORE

THE appearance at the Johns Hopkins Hospital of the following case of acquired tracheoesophageal fistula,‡ the etiology of which was difficult to ascertain, has prompted a review of the literature on this subject. An analysis of all such cases seen at this hospital during the past twenty-five years was also undertaken, and a discussion of the pathogenesis of the disease is contained in this paper.

In 1898, Sirot[1] collected 143 cases of tracheoesophageal fistula. Forty-eight per cent of the fistulas were caused by neoplasms, 12 per cent by inflammatory lesions and 9 per cent by foreign bodies; in 25 per cent the cause was unknown. Of the 456 cases of acquired tracheoesophageal fistula collected from the world literature by Mangabeira-Albernaz[2] in 1933, 80 per cent were caused by neoplasm, 9 per cent by trauma, 5 per cent by syphilis and 3 per cent by tuberculosis. In 1944, Moersch and Tinney[3] reviewed 39 cases of fistula between the esophagus and the tracheobronchial tree. The underlying causes in 46 per cent of these cases were neoplasms, three fourths of which were carcinoma of the esophagus. Thirteen per cent of the fistulas were caused by trauma, 10 per cent by tuberculosis, 10 per cent by syphilis and 5 per cent by diverticulum of the esophagus. In 1950, Coleman and Bunch[4] reviewed 75 cases of acquired nonmalignant tracheoesophageal fistula, 21 of which were taken from the series of Moersch and Tinney. Twenty-eight per cent of these were caused by trauma, 19 per cent by tuberculosis and 15 per cent by diverticulum of the esophagus.

Unfortunately, the diagnoses in many of the cases in these four series were made solely on the basis of presumptive evidence. In some cases, for example, the tracheoesophageal fistula was attributed to syphilis because of a positive serologic test for syphilis and the disappearance of symptoms after antisyphilitic therapy; in other cases the fistula was attributed to tuberculosis on the basis of a positive culture of sputum. The case to be described herein suggests that such evidence may be misleading.

Seventeen cases of acquired tracheoesophageal fistula have been observed at the Johns Hopkins Hospital during the past twenty-five years (Table 1).

Table 1. *Etiology of 17 Cases of Acquired Tracheoesophageal Fistula.*

Carcinoma of the esophagus	7
Carcinoma of the larynx	2
Carcinoma of the bronchus	2
Ingestion of lye	2
Syphilitic aneurysm of the aorta	2
Hodgkin's disease with radiation scar	1
Cause unknown	1

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‡Throughout this article, the term tracheoesophageal fistula will be used to refer to communications between the esophagus and any portion of the trachea or main bronchi.

Eleven of these were caused by carcinoma, 2 by the ingestion of lye and 2 by syphilitic aneurysms of the aorta. In 1 case the fistula occurred after radiation therapy to the mediastinum for Hodgkin's disease; in 1 case the cause, though undetermined, was thought to be either syphilis or tuberculosis. With the exception of this last case and 2 of the cases of carcinoma of the esophagus, the diagnoses in this series were confirmed by microscopical examination of biopsy or autopsy specimens.

It is interesting to note that 86 per cent of the cases of esophageal carcinoma in both the Johns Hopkins series and the series of Moersch and Tinney[3] occurred in males. The average age in both series was fifty-one. In 1 case in the Hopkins series and in 2 of the cases of Moersch and Tinney, carcinoma of the esophagus developed in patients having old lye strictures.

Case Report

G. C. (J.H.H. 583905), a 35-year-old woman, was admitted to the Johns Hopkins Hospital for the first time on September 11, 1951, with the chief complaint of "coughing up" recently ingested food and fluid for the past 5 days.

There was no family history of or known exposure to tuberculosis or syphilis.

Seventeen years prior to admission the patient swallowed the point of a needle, which she had bitten off, but this was apparently expelled. She had had no subsequent dysphagia until the present illness. Nine years prior to admission there was an episode of intermittent, painful swelling of a mass under the left arm. There was no rash at this time, and the swelling gradually subsided, with no further difficulty in the lymphatic system. During the 9-month period prior to admission, there was a 36-pound weight loss, the cause of which was not readily apparent to the patient. There had been no dyspnea, dysphagia, cough, hemoptysis or night sweats. Two weeks prior to admission, the patient developed a head cold with nasal congestion and discharge, lasting 9 days. This was accompanied by a mild cough, productive of thin, yellowish-white sputum. Five days prior to admission, immediately after drinking some water, the patient experienced a strangling sensation and coughed up the water. She next attempted to eat a sandwich, but a few seconds after the first swallow the strangling sensation recurred, and the food was coughed up. For the next 5 days, ingestion of food or drink was impossible, and in order to prevent strangulation on her own saliva, continual expectoration was necessary. At about this same time, 5 days prior to admission, the patient developed chills, fever and a cough productive of foul, yellowish sputum that was occasionally streaked with blood.

On admission to the hospital, the temperature was 102.2°F., the pulse 140, the respirations 20 and the blood pressure 110/80. The patient appeared both acutely and chronically ill, frequently coughing up saliva, as well as foul, yellowish sputum. There were signs of recent weight loss and dehydration. The skin was dry, warm and of fine texture, and the mucous membranes were of fairly good color. There were no abnormalities of the bony framework. Examination of the head was unremarkable. Enlarged lymph nodes were palpable in the submandibular, right axillary, left epitrochlear and right supraclavicular areas. Examination of the chest, lungs, heart, abdomen and neuromuscular system revealed no abnormalities.

The urine was clear yellow, had a specific gravity of 1.020 and gave a + reaction for protein; the sediment contained an occasional white cell per high-power field and no casts. Examination of the blood showed a hemoglobin of 12 gm., a hematocrit of 39 per cent and a white-cell count of 12,600, with a normal differential. The nonprotein nitrogen was 50 mg. per 100 cc. All other chemical determinations of the blood were within normal limits.

Rehydration was accomplished by the parenteral administration of fluids. Because of the possibility of aspiration pneumonitis, the patient was given 1,800,000 units of penicillin daily. A Levine tube was inserted in the stomach to facilitate feeding. Within 3 days the temperature fell to normal. The serologic test for syphilis was found to be positive in a dilution of 1:512 and penicillin was therefore continued at the same dosage.

An x-ray film of the chest showed clear lung fields but increased opacities in the left hilar and right paratracheal regions approximately 5 cm. in diameter. These were presumed to be enlarged lymph nodes. Esophagrams made after the instillation of lipiodol into the esophagus demonstrated a fistula between the esophagus and the first portion of the left main bronchus. Laminographic radiograms later showed that the left hilar mass was causing a narrowing of the left main bronchus, distal to the site of the fistula, by compression from without. Bronchoscopy confirmed the presence of a fistula. Biopsy at this site showed only nonspecific chronic inflammation.

Biopsy of the right supraclavicular node revealed epithelioid tubercles with widespread caseous necrosis. The patient showed no reaction to the intradermal injection of 1:100 dilution of Old Tuberculin. This test was subsequently repeated with a dilution of 1:10, and the patient still showed no reaction. The cerebrospinal fluid showed no cells, 18 mg. per 100 cc. of protein, a positive complement-fixation (Wassermann) test with 0.4 cc. and larger amounts and a normal (flat) mastic curve.

Within 12 days from the time of admission, the axillary and epitrochlear lymph nodes were no longer palpable. No change was seen, however, in the size of the mediastinal masses during fluoroscopy. In order to facilitate the healing of the fistula as well as the feeding of the patient, a gastrostomy was performed.

Bronchoscopic examinations at first showed diminution in the size of the fistulous opening, with considerable clearing of surrounding granulation tissue. The fistula persisted, nevertheless, and local application of silver nitrate proved unsuccessful in stimulating closure. Because the fistula had failed to close, the patient was scheduled for thoracotomy and surgical repair. At the beginning of the 8th week of hospitalization, a sputum culture showed colonies of organisms morphologically identical with *Mycobacterium tuberculosis*. Unfortunately, the guinea pig inoculated with material from the positive culture died in 5 days from causes other than tuberculosis. During the entire course of hospitalization, numerous other specimens of sputum, as well as material from gastric and bronchial aspiration, failed to yield acid-fast bacilli. In addition to 1,800,000 units of penicillin per day, the patient was now given 1 gm. of streptomycin and an average of approximately 12 gm. of para-aminosalicylic acid daily. Three weeks later, at a time when the patient appeared to be in good general condition, two attempts were made to induce her to swallow small quantities of water, but each attempt produced the sensation of strangling and was immediately followed by violent paroxysms of coughing. Soon after the second attempt, the patient vomited her gastrostomy feeding, aspirating the contents. Roentgenograms of the chest revealed aspiration pneumonitis, predominantly of the right lower and middle lobes.

By the 12th week of hospitalization, the acute episode of pneumonitis had subsided but the fistula remained patent. It was decided, therefore, that surgical repair should be undertaken. Accordingly, a left thoracotomy was performed. The fistula was discovered at a point just lateral to the bifurcation of the trachea, between the membranous portion of the trachea and the anterior wall of the esophagus. The esophagus appeared to be pulled down toward the trachea. Although a few lymph nodes were seen at the carina, no lymphoid tissue could be found in the region of the fistula. In the left hilus, 6 cm. from the bifurcation of the trachea, a firm rubbery mass of lymph nodes was found, which was 6 cm. in diameter. This presumably was the mass seen on the roentgenograms of the chest. The fistulous tract, which was about 1 cm. in length, was divided, and the openings in the trachea and esophagus, both of which were 5 to 10 mm. in diameter, were closed. Microscopical examination of the tissue removed with the tract showed acellular connective tissue in some areas and nonspecific chronic inflammation in other areas. Administration of streptomycin and para-aminosalicylic acid was continued for 1 week postoperatively, making a total of 6 weeks of this therapy.

After an uncomplicated postoperative course, during which food was swallowed with ease, the patient was discharged 13½ weeks from the time of admission. After discharge the patient enjoyed good health, gained weight steadily and had no dysphagia. Several attacks of wheezing cough productive of yellowish sputum prompted repeated bronchoscopic examinations, which revealed an increase in granulation tissue at the operative site. A silk suture was removed, together with some granulation tissue, on two occasions. Biopsy and culture of the tissue failed to disclose a specific neoplastic or infectious disease. Subsequent bronchoscopic examinations showed decreasing amounts of granulation tissue. Serial roentgenograms of the chest demonstrated gradual diminution in the size of the left hilar mass.

The patient is being followed in the Out-Patient Department, where she has shown progressive improvement in health. She is at present completely asymptomatic.

Comment. It is reasonably certain that this patient has syphilis. The finding of epithelioid tubercles with massive caseous necrosis in the supraclavicular lymph node and a positive sputum culture for acid-fast bacillus strongly suggests that the patient also has tuberculosis. The concomitant finding of a repeatedly negative tuberculin reaction would have to be regarded as anomalous. There was no evidence, however, of tuberculosis or syphilis in the tissue removed with the fistulous tract.

Site of Fistula

It has been pointed out that the commonest site of tracheoesophageal fistulas is in the region of the bifurcation of the trachea.[3] The left bronchus is said to be involved more often than the right, as might be expected, since the esophagus passes immediately posterior to the left main bronchus and the membranous portion of the trachea as it descends in the mediastinum. Although the case just reported would seem to illustrate this point, analysis of the Johns Hopkins series of cases shows the left and right main bronchi to be involved with approximately equal frequency.

Pathogenesis

Guisez,[5] in an analysis of 706 patients with esophageal disease, found 406 cases of cancer of the esophagus, 162 of which occurred in the middle third of the gullet. Next to mediastinal compression, tracheobronchial perforation was the most frequently encountered complication; it caused a fatal termination in a third of the cases of cancer of the middle third of the esophagus. Carcinoma was the predominant type of malignancy, sarcoma occurring in only 30 cases.

In addition to carcinoma of the bronchus and larynx, both of which caused fistulas in the Hopkins series, carcinoma of the trachea and thyroid,[3] sarcoma of the thyroid[3] and lymphoepithelioma of the hypopharynx[6] have been reported as causing tracheoesophageal fistulas.

Trauma

Next to carcinoma, trauma has been the most frequent cause of tracheoesophageal fistula. Vinson[7] finds that trauma to the esophagus most commonly results from the accidental swallowing of foreign bodies and from the introduction of instruments into the lumen of the esophagus. Among 21 traumatic cases studied by Coleman and Bunch,[4] 4 were caused by foreign body, 4 by dilatation of esophageal stricture, 4 by nonpenetrating wound, 2 by penetrating wound, 2 by operation and 1 by the ingestion of lye. In 4 cases the data were incomplete. Esophagoscopy and gunshot wound have also been reported as traumatic causes of tracheoesophageal fistula.[3]

Inflammatory Disease

Tuberculosis. In 1893, Flexner[8] divided into three groups the cases of tuberculosis of the esophagus that had been reported to that time. First, tuberculosis may arise through continuity or contiguity of structure. Thus, a caseous bronchial gland or an abscess associated with caries of the spine may ulcerate and perforate the esophagus. Secondly, a pre-existing lesion, — for example, an old lye stricture, — is regarded as predisposing to the tuberculous infection. Thirdly, infection may be brought to the esophagus by the blood stream or by direct contact with the swallowed sputum. In 16,489 autopsies performed on tuberculous cadavers, Lockard[9] was able to find only 25 cases in which the esophagus was involved.

According to Rich,[10] caseous bronchitis can almost invariably be shown to be secondary to a focus of infection in a related portion of the lung or to encroachment from without by an adjacent caseous lymph node. Silverman,[11] in a study of 110 consecutive autopsies performed on patients with tuberculosis severe enough to cause death, was able to find tuberculosis of the trachea or bronchi in 60 per cent of the cases. Because the trachea or bronchi were most frequently involved in those cases having large pulmonary cavities and therefore more abundant quantities of bacilli-laden sputum, she considered direct surface implantation the most likely mode of infection. Rich[12] points out that in cases of massive and long-standing infection secondary pyogenic infection is likely to occur. He suggests that the infection of the bronchial wall by the tubercle bacilli present in the lumen may occur only at sites where the bronchial epithelium has been destroyed by pyogenic infection or by a hypersensitive reaction.

Bugher, Littig and Culp,[13] in a thorough study of 122 cases of pulmonary tuberculosis coming to autopsy, found the tracheobronchial tree to be involved in 48 per cent of cases. The relatively infrequent involvement of the tracheobronchial mucosa in those cases showing miliary dissemination led them to the conclusion that the hematogenous route is of little consequence in the establishment of these lesions. In analyzing their cases of tracheal tuberculosis, they found many instances of mucosal involvement in which both the peritracheal connective tissue and the adjacent lymph nodes were free of any evidence of disease, which led them to the conviction that tracheal

involvement is predominantly a matter of direct implantation.

Paviot, Levrat and Guichard[14] reported a case in which tuberculosis of the esophagus perforated into the trachea, without evidence of a pulmonary lesion. Lockard[9] was able to find only 1 reported case in which a tuberculous esophageal ulcer perforated into the respiratory tract. There were enlarged bronchial glands in that case. Coleman and Bunch[4] have never observed ulcerative tracheobronchial tuberculosis to lead to fistulous communication with the esophagus in the absence of mediastinal tuberculous lymphadenitis. It may be that the crucial factor in the formation of fistulas between the two is the presence of tuberculous mediastinal lymph nodes whether the tuberculosis first involves the esophagus or tracheobronchial tree. Fistulas between the esophagus and the trachea may also result from ulceration and perforation of tuberculous diverticula (a situation in which tuberculous lymphadenitis undoubtedly plays a prominent role) and from a tuberculous empyema of long standing.[15]

Syphilis. In Abel's[16] experience, syphilis causes only 0.1 to 0.2 per cent of all esophageal lesions. In 1924, Guisez[17] was able to collect only 6 or 7 cases from the literature. In over 3000 esophagoscopic examinations, he made a definite diagnosis of esophageal syphilis in only 1. In a review of the world literature from 1717 to 1930, Guyot[18] found 55 cases of syphilis of the esophagus, to which he added 2 of his own. Autopsies were performed in only 11 cases, with confirmation of the diagnosis by microscopical examination in only 3. The diagnosis in 15 other cases depended only on recognition during esophagoscopy coupled with a good response to antisyphilitic therapy. The remainder were even less conclusively demonstrated. Hudson and Head[19] were able to find 20 additional reported cases between 1930 and 1950. Unfortunately, the diagnosis in many of these cases also seems to have depended solely on a positive serologic test for syphilis and improvement after antisyphilitic therapy.

During the secondary stage, according to Abel,[16] syphilis may give rise to an esophagitis of sufficient severity to produce marked dysphagia. Late syphilis may take the form of an ulceration, a submucous gumma or a diffuse inflammation within the esophageal wall. The esophagitis tends to occur in the middle half of the esophagus[20]; gumma usually arises in the upper or lower third of the esophagus.[16] Finally, there may be direct extension of the syphilitic process from a neighboring organ or tissue, such as the aorta, a mediastinal lymph node, the lung or the sternum. Wilcox[21] considers this the most frequent mode of invasion.

In 1903, Conner[22] reviewed 128 cases of tracheobronchial syphilis and pointed out that the tracheal and bronchial manifestations of secondary syphilis are so fleeting in character that for all practical purposes the lesions may be said to be confined to the late stages of the disease. Of the 117 patients in Connor's series in whom the character of the lesion could be determined 17 per cent had gummas, 44 per cent ulcers, 51 per cent overgrowths of endotracheal connective tissue and 7 per cent fibrous peritracheitis.

Syphilis may cause tracheoesophageal fistula in at least two different ways, according to Clagett, Payne and Moersch.[15] A gumma of the esophagus or tracheobronchial tree (by ulceration and perforation) or a syphilitic aneurysm of the aorta (by pressure necrosis) may lead to a communication between the trachea and the esophagus. In 128 cases of tracheobronchial syphilis, Conner[22] was able to find only 2 instances of fistula formation, both of which had resulted from perforation of tracheal ulcers into the esophagus. In 1934, Lukens and Ono[23] reported a case of syphilitic tracheoesophageal fistula. They were able to find only 12 other cases in the literature. In at least 3 of these the diagnosis of syphilis was not definitely established.

Actinomycosis. A few tracheoesophageal fistulas caused by actinomycosis have been reported.[2, 3, 24]

Empyema. Berman and Walters[25] reported a case of empyema complicated by bronchoesophagopleural fistula. Since this case has been referred to by others as an illustration of tracheoesophageal fistula caused by nontuberculous empyema, it should be stated that Berman and Walters were not certain whether the tracheoesophageal fistula was the cause or the result of the empyema.

Diverticulum of the Esophagus

In reviewing over 15,000 consecutive autopsies performed at the Johns Hopkins Hospital, we were able to find only 23 cases of esophageal diverticulum below the pharyngoesophageal region. Twenty-one occurred in the midportion of the esophagus in the region of the bifurcation of the trachea, and at least 14 of these were definitely of the traction type. This is the type of diverticulum that is most likely to be complicated by a tracheoesophageal fistula.[26]

Although it has been presumed by many that tuberculous mediastinal lymphadenitis is the commonest cause of traction diverticulum, analysis of the 23 cases above shows that the diverticula were adherent to tuberculous mediastinal lymph nodes in only 4 cases. Although there were no signs of granulomatous inflammation adjacent to the diverticulum in 4 other cases, there was tuberculosis elsewhere in the chest. In 3 cases the diverticulum was found near a syphilitic aneurysm of the aorta, and adhesions could be seen between the two structures in 1 of these. No specific underlying cause could be determined in 12 cases.

In addition to the causes found in this series, diverticulum of the esophagus is said to have been

associated with adhesions in the vicinity of caries of the spine and pericarditis[27] and with a suppurative lung abscess.[28]

Tracheoesophageal fistula secondary to a diverticulum of the esophagus results when the pouch becomes infected, ulcerates and perforates the tracheobronchial tree. In the series of 23 cases just discussed, there were no instances of tracheoesophageal fistula, indicating the relative infrequency of such fistulas as complications of diverticulum of the esophagus. Jenkinson and Bate[29] were able to find only 5 reported cases of fistulous communication between an esophageal diverticulum and the tracheobronchial tree. Coleman and Bunch[4] collected 11 reported cases but observed that it was not always possible to identify the initial infection.

The very nature of these pathologic processes precludes elucidation in many instances. Thus, during the active process of formation of traction diverticulum or tracheoesophageal fistula, when, more commonly than not, the patient is asymptomatic, the causative agent may be evident, but by the time the process is complete and symptoms are more likely to have become prominent, one may be able to find only connective tissue and nonspecific chronic inflammation.

Coexistence of Diseases

Although it is generally considered wiser to attempt to explain a given illness on the basis of a single disease process, one is occasionally forced to recognize that two or more pathologic processes are to be found within a single lesion. In 1904, Jackson[30] reported a case in which he was certain that carcinoma, syphilis and tuberculosis coexisted in the larynx. In 1916, Dean and Gregg[31] reported a case of coexistent carcinoma, tuberculosis and syphilis of the esophagus. Biopsy of the lesion gave definite proof of tuberculosis and carcinoma. The sputum contained tubercle bacilli and the serologic test for syphilis was positive. Because of the marked improvement in swallowing soon after the institution of antisyphilitic therapy, it was presumed that syphilis was also present in the lesion. In 1950, Brackett and Lautz[32] described a case of double malignant tumor associated with pulmonary tuberculosis and esophagobronchial fistula. In this case there was carcinoma in the larynx as well as in the esophagus, where it caused the fistula. In addition, the lungs were filled with areas of caseous tuberculosis. Here, then, was a case in which a positive sputum culture for acid-fast organism might have led to an erroneous diagnosis of the underlying cause of the fistula.

The possible coexistence of syphilis and tuberculosis in the patient here reported brings up the question of the relation of these two chronic diseases. The evidence to date, both clinical and experimental, indicates that syphilis exerts no appreciable influence on the course of tuberculosis.[33]

Symptoms

Regardless of the underlying cause, once the tracheoesophageal fistula is established, the most characteristic symptom, — and, indeed, the only one that is pathognomonic, — is a sudden strangling sensation a few seconds after the ingestion of food or drink. This is followed immediately by a severe paroxysm of coughing, during which the ingested material may be coughed up. Even with this dramatic sequence of events, one must be certain that material is not entering the larynx directly. When this occurs, choking is likely to begin with deglutition, whereas with tracheoesophageal fistulas there is a short but definite pause before the sensation of strangling occurs.[34]

The size, site, direction and underlying cause of the fistula will determine the nature and course of the symptoms. With a small fistulous opening in the esophagus, solids, in contrast to liquids, may be taken without strangling. Sometimes a piece of food will plug the fistulous opening, thus allowing the patient to drink without choking.[34] Often it is found that strangulation can be avoided by eating in a recumbent position, gravity acting as a safeguard.[23] Hemorrhage from the mouth is not an unusual symptom and may be the terminal episode, as in one of the cases in the present series. In untreated cases, chronic cough, frequent infections of the upper respiratory tract and recurrent pneumonia are common.[4]

Weight loss and general debilitation are frequent findings, but they are of little help in differential diagnosis, as they occur in cases of chronic infection as well as of neoplasm.

Increasing dysphagia for some time prior to the onset of strangulation is a frequent occurrence in those cases in which the underlying cause of the fistula is carcinoma. In the present series this ranged from one to six months in duration. Progressive dysphagia may also be the only sign of syphilis of the esophagus.[18] The history or signs of trauma antedating the onset of strangulation should certainly suggest the possibility of tracheoesophageal fistula. A history of prolonged and indefinite illness may be the only manifestation in those cases due to tuberculosis or syphilis. Although Vinson[35] has found that traction diverticula of the thoracic esophagus rarely produce symptoms, Wallace,[36] in a series of 26 patients, found symptoms present in a little over a third of the cases. Substernal distress, dysphagia and hemorrhage from the mouth were the symptoms most commonly encountered.

Although the symptoms associated with the establishment of a tracheoesophageal fistula are usually severe, Jenkinson and Bate[29] reported a case in which symptoms referable to the fistula had been present for five years before medical aid was sought.

Diagnosis and Treatment

Demonstration of the fistula usually presents no difficulty once the possibility of tracheoesophageal fistula is entertained. Roentgenographic studies are most helpful and should include a regular chest x-ray examination, chest fluoroscopy and x-ray films made after the instillation of a contrast medium, laminograms and bronchograms. Iodized oil rather than barium should be used as a contrast medium because it is less irritating to the lung. One should be sure that the contrast medium does not overflow from the esophagus into the larynx, since this may produce a roentgenogram simulating that of fistula. Roentgenographic demonstration of the fistula may be facilitated by the direct instillation of iodized oil into the esophagus while the patient is in the prone position. Once the oil has entered the trachea, an erect lateral roentgenogram will give the best view.[37] Bronchoscopy and esophagoscopy, in addition to confirming the presence and site of the fistulous openings, enable one to take specimens for biopsy and culture. Of the many studies that may be made to determine the underlying cause of the fistula, direct biopsy and culture of the lesion, when positive, will be the most conclusive.

Treatment, naturally, will depend on the underlying cause of the fistula. When this is amenable to treatment, healing of the fistula may be facilitated by cauterization. Clerf, Cooley and O'Keefe[38] have reported prompt closure of the esophageal end of the fistula in cases caused by nonspecific inflammation, after the introduction of beads of sodium hydroxide into the lumen of the fistula for three minutes. The creation of a gastrostomy in the more refractory cases will facilitate both the healing of the fistula and the feeding of the patient. Analysis by Coleman and Bunch[4] of 75 cases of nonmalignant tracheoesophageal fistula shows that surgical therapy, in the form of either cauterization or direct surgical repair, has resulted in a much higher cure rate than nonsurgical treatment. One anticipates even better results with the aid of the new antibiotics. Counteracting any optimism, however, is the possibility of carcinoma, the most frequent cause of tracheoesophageal fistula and at present the least amenable to treatment.

Summary

An acquired tracheoesophageal fistula of undetermined etiology was encountered in a thirty-five-year-old woman with syphilis and probably tuberculosis. The fistula was satisfactorily treated by surgical intervention.

The main causes of acquired tracheoesophageal fistula, in order of frequency, are carcinoma, trauma, syphilis and tuberculosis.

The commonest site of the tracheoesophageal fistula is in the region of the bifurcation of the trachea.

A sudden sensation of strangling a few seconds after the ingestion of food or drink is the most characteristic symptom of tracheoesophageal fistula.

The fistula can be demonstrated by roentgenograms of the chest made after the instillation of iodized oil in the esophagus. Specimens for biopsy and culture may be taken during the esophagoscopic and bronchoscopic examination of the fistulous openings.

Closure of the fistula is best accomplished by an adequate course of chemotherapy, local cauterization and surgical intervention.

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MEDICAL INTELLIGENCE

CYSTITIS EMPHYSEMATOSA*

Case Report with Clinical Diagnosis and Review of the Literature

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CYSTITIS emphysematosa is a rare urologic disease. Its rarity may be more apparent than real. Mills has defined it as an "emphysematous condition of the bladder wall associated with cystitis and hemorrhage."[1]

The presence of gas in the bladder wall is not a unique situation in the human being, for pneumatosis intestinalis and colpitis emphysematosa in women occur not infrequently. They are apparently not part of the same condition. Various domestic animals have been shown to have the disease.[2]

In man the majority of cases of cystitis emphysematosa have been observed at autopsy. Approximately 50 cases have been reported in the literature. Only 13 cases have been diagnosed ante mortem.[3]

Several workers have contributed significantly to our understanding of this entity. Eisenlohr (1888) described the first human case and described extensively the miscroscopical, pathologic and etiologic features.[4] Lautenschlager (1911) may have been the first to diagnose the disease cystoscopically, but he described it as "cystitis" in the ante-mortem record.[5] Hueper (1926) collected the first 11 autopsy reports, all in women, and observed it in a female dog.[2] Mills (1930-1932), in a brilliant series of five articles with 12 cases, publicized the disease and discovered its existence in males. He described the pathology and pointed out that this was not a post-mortem occurrence but existed ante mortem and would eventually be diagnosed in the living.[1, 6-9] Ravich and Katzen (1932) are credited with the first ante-mortem diagnosis and recovery in a patient in whom a cystotomy was performed for profuse hematuria.[10] Redewill (1934) reported 2 cases and established a precise classification, clarifying the disease and cataloguing it. In addition, he advised the use of oxygen cystograms to outline the bladder for radiographs and to demonstrate the cysts as less dense areas in the bladder outline. He further developed a device for collecting the gas from the cysts.[11] Burrell (1936) reported the first case seen cystoscopically and then reproduced the disease experimentally, using chemical vesical trauma and introducing bacteria.[12] Lund, Zingale and O'Dowd (1938) described the radiolucent ring about the bladder as a specific diagnostic feature of the disease. They also identified the gas present in cysts as carbon dioxide.[13]

Since then, cases have been reported from time to time in the literature. Thirteen cases have been identified ante mortem to date. Only 5 cases have demonstrated a radiolucent ring by x-ray.[11, 13-16] The case reported here is the sixth case to demonstrate this specific pathognomonic finding.

The etiology has not been conclusively established. Bacteria of the colon group have been implicated in the majority of cases. Many cases have been associated with diabetics or with patients who had normal sugar values but had received considerable intravenous glucose therapy. The presence of *Cl. welchii* has been observed in a few cases.[17]

The four groups of Redewill, classified etiologically, may be used as a guide.[11]

Group 1. Fulminating anaerobic bladder emphysematous cases due to gas bacillus, terminating fatally with virulent generalized infection. Gas is seen in all the vesical coats.

Group 2. Bacillus coli cystitis — in these cases *B. coli* have been found in the bladder wall, involving the mucosa and submucosa. These patients may recover.

Group 3. In these cases no bacteria are found in the bladder wall, yet there is a general dissemination of gas in the superficial and deep layers of the bladder. This is found in diabetics with blood sugar of 200 mg. or more per 100 cc. of blood. This type has been produced experimentally in the intestinal mucosa and serosa of young animals, as demonstrated by Rossi.[11] Perhaps an enzyme liberated in the submucosa acts on the glucose and liberates carbon dioxide, a known constituent of the cysts.[11]

Group 4. Circumscribed groups of gas-containing cysts lie in the mucosa of the bladder wall with no evidence of bladder-wall infection. They resemble the intestinal cysts with a wall of endothelium but are not manifestations of emphysema. Bacteria play no part in the formation of this group, as no inflammation is observed around the cysts.

Trauma has been considered in cases in which catheters, cystoscopes and other instruments have damaged the bladder and air or gas-producing organisms have been introduced under the epithelium.[18] Burrell has succeeded in producing the disease by damaging a rabbit's bladder with silver

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nitrate, giving the rabbit glucose injections and then introducing colon bacilli from a patient with cystitis emphysematosa.[12]

In most cases in which a hemorrhagic *B. coli* cystitis exists with marked debility of the patient and desquamation of the surface vesical epithelium, it is considered that enzymes produced by the organisms enter the submucosa and produce gas from the excess glucose present.

A generally debilitated patient with focus of bacteria, proper tissue pH, trauma to the bladder and urinary-tract obstruction may develop this disease.

The pathology has been well described by Mills.[1, 6-9] It is an inflammatory condition of the bladder, acute or chronic, and is associated with the presence of gas vesicles in the tissue. The gas vesicles may cover the surface of the bladder locally or diffusely. They usually involve the mucosa and submucosa and, in extreme cases, the deeper layers of the bladder. The vesicles appear grossly independent of one another but microscopically are seen to be freely intercommunicating and confluent.

Inflammatory changes may be pronounced; these include leukocytic infiltration, necrosis, hemorrhage, stasis and formation of giant cells. The lymphatics may be dilated and compressed; blood vessels may rupture. The involved bladder wall is usually thickened. The mucosa may appear normal except for the cysts or may be fiery red with hundreds of small spherical vesicles, varying from 1 mm. to 1 cm. in size.

Bacteria may be observed in stained sections of the bladder.

The clinical features vary. Many cases reported showed no urologic symptoms. In the cases diagnosed cystoscopically a colon-bacillus hemorrhagic cystitis was the usual cause of the investigation.

Bloody and frequent urination is common. In several cases pneumaturia and bloody urine were noted. Hall observed suprapubic crepitation after transurethral prostatectomy in 3 cases in which at autopsy, shortly afterwards, numerous cysts were observed in the bladder.[19] Pyuria and severe dysuria have also been observed.[20]

The majority of cases have occurred in diabetics. However, in many reported cases the urinary picture developed as a late event in the terminal stages of cholecystitis and cholelithiases, after operation, and in cases with peritoneal soilage, subdiaphragmatic abscess and so forth.

Many cases were observed unexpectedly at cystoscopy. Other were diagnosed by the radiolucent ring in the excretory urogram. Five cases have been so diagnosed. This is the only form of cystitis that can be specifically diagnosed radiologically; the ring is absolutely pathognomonic of the disease.[21] However, both the vesicles and the ring are transient phenomena. Patients cystoscoped twenty-one and seven days before death revealed no cysts yet were observed to have them at autopsy. Burrell[12] demonstrated, by repeated cystoscopy, that all cysts tended to disappear in a few days. Hence the cystoscopic and radiographic diagnosis is often pure chance, depending on the stage of the disease.

Case Report

A. H. (A87448), a 66-year-old man, was admitted to the Surgical Service, complaining of lower-abdominal pain, nausea, vomiting and infrequency of bowel movements. A weight loss of nearly 50 pounds had occurred in the past year. He had eaten no solid food for 1 week for fear of aggravating the abdominal pain. Chills and fever occurred 4 days before admission. There were no urologic symptoms.

Past and family history were noncontributory.

At physical examination the temperature was 98.6°, the pulse 76 and the respirations 20. The patient was dark and moderately obese, alert and co-operative. The skin and body revealed poor hygiene. The teeth were carious. The lungs were clear and the heart normal. The abdomen was obese, with tympany in the upper abdomen and tenderness in the right lower quadrant. The prostate was enlarged + rectally.

Laboratory examination of the blood revealed a red-cell count of 4,430,000, a hemoglobin of 14.5 gm. and a white-cell count of 11,150, with 81 polymorphonuclear leukocytes. The urine was amber-colored, with a specific gravity of 1.027, acid and negative for sugar, acetone and albumin. Microscopically, it showed numerous white cells, free and in clumps. The blood sugar was 62 and the nonprotein nitrogen 42. A blood Wassermann test was negative. There was occult blood in the feces; urinary-bile studies were negative. X-ray studies revealed cholelithiasis and a filling defect in the cecum and terminal ileum.

On March 26, 1949, a right colectomy with ileotransverse colostomy and cholecystectomy were performed by the surgical staff. The condition was reported as diverticulitis and chronic cholecystitis with no malignancy.

On the 4th postoperative day, the patient became distended, with generalized abdominal tenderness. X-ray films revealed small-bowel obstruction on the left side. The nonprotein nitrogen was 54. Urine showed +++ sugar and 20 to 25 white cells per high-power field. Surgical exploration revealed obstruction, and a Witzel enterostomy was performed. A Miller–Abbott tube was passed.

Ten hours after this operation, difficulty in voiding developed. Attempts at catheterization with rubber catheters and later with rubber catheters with stylet were unsuccessful and resulted in considerable urethral bleeding. Subsequently, the patient voided spontaneously in 200-cc. quantities. He then became disoriented. His temperature rose to 102°; the pulse was 124, the respirations 24 and the nonprotein nitrogen 59.

Over the next 48 hours, he developed severe shaking chills with fever to 105°. On the 3rd postoperative day, his temperature rose to 106° after a chill, and his condition became critical. The blood pressure was recorded as 70/30 and the pulse as 142. He became comatose and then rallied.

On the 6th postoperative day, his urine showed numerous white cells and rare red cells. On the 7th postoperative day, his temperature rose to 106.8° after a chill. The white-cell count was 21,800, with 90 segmented neutrophils. On the 10th postoperative day, he had another chill, with the temperature rising to 106°.

Malaria smears, blood culture and all agglutination studies were negative. The fever continued to spike every 3rd day, with gradual tapering off to normal.

On the 11th postoperative day, roentgenograms of kidney, ureter and bladder and intravenous urograms revealed a small bladder, irregular in outline, consistent with the picture of cystitis.

On the 13th postoperative day, at urologic consultation, examination of the patient revealed urethral obstruction. Attempts to catheterize the bladder were unsuccessful. Review of the films revealed on the flat plate a radiolucent ring of air that completely outlined the bladder as it filled with the intravenous dye (Fig. 1, A and B). Accordingly, a

radiologic diagnosis of cystitis emphysematosa was made. Urination was frequent and bloody; hence urine and blood cultures were taken.

On the same day the temperature rose to 107.6°; the pulse was 150. There was profuse diaphoresis and a clear sensorium. Blood was again taken for culture.

The patient was transferred to the Urological Service and a suprapubic cystotomy was performed. The previous diagnosis of cystitis emphysematosa was confirmed.

There was no evidence of perivesical suppuration or extravasation. On incision of the bladder wall gas escaped and

FIGURE 1. *Roentgenograms Showing Radiolucent Ring of Air Outlining the Bladder.*

bloody urine poured out of the bladder. Cultures were taken. The bladder mucosa was diffusely hemorrhagic. Sections of the bladder wall were taken for pathological study. There was hypertrophy of the middle lobe of the prostate gland.

The bladder cultures were reported as revealing *Bacillus coli;* the pathologic studies disclosed cystitis cystica.

The patient's recovery was uneventful until three weeks after the cystotomy; on May 12, 1949, he again developed small-bowel obstruction and underwent laparotomy for lysis of adhesions.

He was discharged on June 1, 1949, voiding well. He is at present asymptomatic.

Discussion and Comment

The apparent rarity of this disease is attributable to the many factors involved in its genesis and to its transient appearance — either terminally after a debilitating illness or in the course of an extremely hemorrhagic *B. coli* urinary infection. Thus, the custom of taking only one set of films in the average urologic case, minimizes the opportunity of seeing more patients with radiographic evidence of the condition.

Diabetics have been shown to have a high incidence of latent urinary infection.[22] In these patients the presence of urinary obstruction, such as prostatism, might produce an intermittent, closed-off urinary infection and lead to the syndrome described in this paper. Cholelithiasis, cholecystitis or some enteric infection has been noted to occur in a high percentage of patients and is especially significant in that it may be the primary cause of infection of the urinary tract postoperatively when the patient is recumbent, with bladder decompensation or with mechanical obstruction requiring catheter intervention. The addition of multiple glucose infusions aggravates the condition.

The diagnosis must be considered as a remote possibility in urinary infections occurring at any age, as it has been reported in early infancy as well as in the aged.[20]

Therapy consists of adequate care of the primary surgical problem, gall-bladder disease or initial enteric disease, with the removal of urinary obstruction, identification of the predominant organism by culture and subsequent specific chemotherapy or antibiotic therapy as indicated. In diabetics, the blood sugar must be well regulated and kept well below the critical level of 200 mg. per 100 cc.[11]

In patients with discrete vesicles and no active inflammation, the disease is self-limited[12] and requires no treatment unless obstructive uropathy is present. Local treatment of the vesicles is superfluous.

Summary

A case of cystitis emphysematosa in a sixty-four-year-old man, with clinical diagnosis and survival, is reported.

This is the sixth case diagnosed by the radiolucent ring about the bladder wall on cystography and the fourteenth case in which diagnosis was made ante mortem.

The literature is reviewed and the clinical features of the disease are briefly discussed.

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PROTECTION OF CARDIAC GLYCOSIDES FROM ACTION OF LIGHT BY ACTINIC DESENSITIZER (RED DYE)

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DIGITALIS, in solution, has a limited shelf-life. The major cause of deterioration is absorption of actinic rays. This is especially true of green solutions. Elimination of green coloring matter and protection from actinic rays by an internal red dye have yielded tinctures with remarkable keeping power.

PREPARATION

A stabilized tincture of digitalis may be prepared that can be dispensed in clear-glass bottles and kept at effective strength in a daylighted place for much longer periods of time than U.S.P. tincture. All of the green coloring matter is removed by animal charcoal by contact procedures (mixing and filtering). After this, a red coloring matter is added — either aniline red or phenyl-safranine. Aniline red is preferred; it may be obtained in the form of approved F. D. & C. dye for food use. It is essential that after decolorization and treatment with the dye the tincture must be restandardized to U.S.P. strength and adjusted for any deviation.

TESTS PERFORMED

Experimental tests were performed in order to compare the keeping qualities of tincture of digitalis with these especially prepared tinctures that contain actinic desensitizers.

All potency tests were performed in accordance with the U.S.P. XII. This is the Hatcher–Brody cat method.*†

The materials used were tincture of digitalis, U.S.P. XII; tincture of digitalis especially prepared for inclusion of actinic desensitizer as outlined above (a decolorized solution without inclusion of the actinic desensitizer); a solution decolorized according to the method outlined above, together with 0.1 per cent phenyl-safranine; a decolorized solution made according to the method outlined above containing 0.1 per cent amaranth red (F. D. & C. red No. 2).

All solutions were adjusted to 104 per cent prior to testing. The test procedure consisted of placing each of these solutions in three separate bottles. One sample of each was put into the amber-brown bottle of commerce (in which tincture of digitalis is usually distributed). Another sample of each was put into a clear-glass bottle, the ordinary flint glass of commerce. Each of these was placed on the laboratory shelf and exposed to the usual room conditions. Each sample solution was put into a clear flint flask and subjected to irradiation to the extent of one erythema dose from a cold quartz lamp once monthly and was alternately switched from an incubator at 35°C. to a refrigerator at 5°C. at monthly intervals. This provided an accelerated keeping test.

RESULTS

The results are summarized in the following tables and in Figure 1.

Tincture of Digitalis, U.S.P. XII

TIME	BROWN BOTTLE	CLEAR BOTTLE	CLEAR BOTTLE PLUS EXPOSURE AND IRRADIATION
	%	%	%
Before keeping test	104	104	104
After 6 months	80	60	44
After 1 year	78	63	
After 1½ years	64	58	
After 2 years	50	50	

Decolorized Solution

TIME	BROWN BOTTLE	CLEAR BOTTLE	CLEAR BOTTLE PLUS EXPOSURE AND IRRADIATION
	%	%	%
Before keeping test	104	104	104
After 6 months	92	82	50
After 1 year	90	82	
After 1½ years	85	64	
After 2 years	81	60	

**U. S. Pharmacopoeia XII.* Easton, Pennsylvania: Mack Publishing Company, 1942. Pp. 50 and 51.

†The older edition of U.S.P. was utilized because of the need for uniform test procedure. These tests commenced three years ago. In the meantime, the later edition of U.S.P. has changed the method of standardization.

Decolorized Solution Plus 0.1% Phenyl-Safranine

Time	Brown Bottle	Clear Bottle	Clear Bottle Plus Exposure and Irradiation
	%	%	%
Before keeping test	104	104	104
After 6 months	90	88	75
After 1 year	90	88	
After 1½ years	74	80	
After 2 years	70	75	

Decolorized Solution Plus 0.1% Amaranth Red, U.S.P. XII

Time	Brown Bottle	Clear Bottle	Clear Bottle Plus Exposure and Irradiation
	%	%	%
Before keeping test	104	104	104
After 6 months	96	95	82
After 1 year	94	93	50
After 1½ years	89	90	
After 2 years	80	90	

Summary and Conclusions

It will be seen from the tables that tincture of digitalis deteriorates within a year under ordinary conditions. When in clear-glass bottles or under unusual keeping conditions deterioration to a level below the U.S.P. requirement may occur in three to six months.

Decolorized solutions (in respect to green coloring matter) last for a longer time.

Decolorized solutions, to which an internal actinic desensitizer has been added in the form of a red dye,

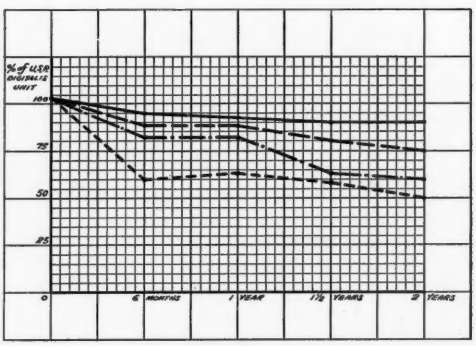

Figure 1. *Results of Test for Protection of Cardiac Glycosides.*

——— Decolorized solution plus amaranth red.
— — — Decolorized solution plus phenyl-safranine.
· _ · _ Decolorized solution.
- - - - Tincture of digitalis.

have at least twice the shelf-life of the standard tincture.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38231

Presentation of Case

A sixty-one-year-old woman entered the hospital because of swelling of the abdomen and legs.

Twenty years before admission, the patient began to have occasional episodes of shortness of breath; examination by her family physician revealed irregular rhythm of the heart. Ten years prior to entry, the patient started to take digitalis. Edema of the legs appeared for the first time four years before admission. Examination then showed marked edema of the legs and signs of fluid in the right chest and abdomen. The heart was enlarged; there was a Grade III musical systolic murmur and a rumbling diastolic murmur over the apex. The liver was enlarged. The electrocardiogram showed auricular fibrillation with a ventricular rate of 72 per minute. There was right-axis deviation and an occasional ventricular premature contraction. Since then, the patient had been on a low-salt diet, daily digitalis and injections of a mercurial diuretic twice a week. During the six months before admission, the shortness of breath increased somewhat, but otherwise the patient was well. Ten days before entry, the abdomen became bigger and the edema of the legs worse, and the patient failed to respond to diuretics.

The patient had had chorea at the age of seven. She had had two pregnancies, both uneventful.

Physical examination revealed a dyspneic, emaciated woman. The neck veins were distended and pulsating. There were moist rales in the left lower chest and dullness and decreased breath sounds in the right base. The heart was enlarged to both sides. Grade III systolic and diastolic murmurs were heard over the whole precordium, but loudest at the apex and aortic area. The systolic murmur was audible over most of the chest and was transmitted to the neck. The rhythm was irregular. The abdomen was distended with a demonstrable fluid wave. The liver was palpable three fingerbreadths below the costal margin; it was nonpulsatile and seemed to have a nodular surface. Marked edema involved both lower extremities and sacral region.

The temperature was 98.4°F., the pulse 80 per minute and irregular, the respirations 22 and the blood pressure 130 systolic, 70 diastolic.

The urine had a specific gravity of 1.015 and gave negative reactions for albumin and sugar; the sediment contained occasional white cells and hyaline and granular casts per high-power field. Examination of the blood disclosed a hemoglobin of 12.2 gm. per 100 cc. and a white-cell count of 13,700, with 92 per cent neutrophils. The nonprotein nitrogen was 48 mg., the total protein 4.94 gm., the albumin 3.07 gm., the globulin 1.87 gm., the calcium 9.1 mg., the phosphorus 3.5 mg. and the phosphatase 3.3 units per 100 cc.; the sodium was 123.5 milliequiv., the potassium 4.2 milliequiv., the chloride 96 milliequiv. and the carbon dioxide 36.6 milliequiv. per liter. The electrocardiogram showed evidence of right ventricular hypertrophy and auricular fibrillation. The roentgenograms revealed fluid in the right pleural cavity. There was either a mass behind the heart or a markedly enlarged left auricle displacing the left main bronchus upward (Fig. 1). The visualized portion of the lung fields was clear. The eighth and eleventh thoracic and the first lumbar vertebras showed wedging of the bodies. All the visualized ribs, vertebras and pelvic bones were markedly decalcified without localized bone destruction.

FIGURE 1.

On the second hospital day, 350 cc. of abdominal fluid and 400 cc. of chest fluid were aspirated. Both ascitic and pleural fluid were cloudy yellow. The former contained 42 white cells and 1013 red cells per cu. mm.; the latter, 43 white cells and 526 red cells. The patient was treated with digitoxin, Mercuhydrin and aminophylline, but she grew steadily worse and died on the fourth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD F. BLAND*: Before I start, Dr. Wyman, would you clear up the question of the mass either behind or in the heart mentioned in the record.

DR. STANLEY M. WYMAN: I do not know how much I can clear it up, Dr. Bland. The patient was obviously very sick. The heart shadow is tremendous, extending nearly to the chest wall on the left, and well into the right lung field (Fig. 1). The left main bronchus is quite well seen, being pushed upward. The pleura in the right pleural space is adherent. The lateral film is totally unsatisfactory. I should be inclined to think the shadow described was the left auricle, but I do not know any way to be certain in an individual too sick to be fluoroscoped or examined in adequate fashion.

DR. BLAND: I wonder why the question of a mass was raised here. This is almost certainly a giant left auricle.

DR. WYMAN: I do not know; I also think it is a large left auricle.

The collapsed vertebral bodies can be seen in the lower thoracic region and in the midthoracic region. There is an interesting cluster of calcium in the right lower abdomen that could represent gallstones. I think there is evidence of ascites.

DR. BLAND: How do you interpret the appearance of the bones?

DR. WYMAN: I should be inclined to think of senile osteoporosis with slight compression fractures, bearing in mind the fact that widespread bone-marrow disease such as multiple myeloma or metastatic carcinoma cannot be excluded.

DR. BLAND: I suppose the physicians in charge here were pursuing that thought because of the hint about the hard liver and the phosphatase determination.

As I went over this history my first reaction was: I wonder why I am to discuss this case; that put me on guard. It looks like a straightforward course, a rather favorable course, for a patient with chronic rheumatic heart disease who had been well treated over a long period of time, with survival to sixty-one years of age. This patient, who had been fibrillating for ten years, got along quite well until near the end. Ten years is not extreme; a few patients with rheumatic heart disease have fibrillated for thirty years, but ultimately some complication arises.

Intracardiac thrombosis, peripheral embolism, peripheral thrombosis and pulmonary embolism are common complications in older patients with long-standing valvular disease. I think the figures from the Department of Pathology[1] indicate that in persons of this age who die of rheumatic heart disease, pulmonary embolism and infarcts are found in somewhere between a third and a half of

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cases at post-mortem examination. There is no clear evidence that such occurred in this patient. In any patient with rheumatic heart disease, complicating infection is probably the chief hazard through life, either reactivation of the rheumatic state or bacterial endocarditis. Certainly there was no evidence here of bacterial endocarditis or of reactivation of the rheumatic state. It appears that we may soon have to revise somewhat our concepts as to what constitutes an active rheumatic state, because the surgeons in the last two to three years have given us an opportunity to study biopsies at operation on patients with mitral stenosis, and close to 25 per cent of the auricular appendages show active Aschoff bodies; yet in the majority we have no clinical clue before operation that they have active rheumatic disease.

In the reverse direction, one might ask why this patient did so well for so long. This is perhaps of even more importance than why she died. Which types of valvular disease are best borne? Those who have predominantly mitral regurgitation usually get along quite well. Eventually they may develop a large left auricle — all the giant auricles are related predominantly to regurgitation rather than to stenosis. Some patients who develop tricuspid insufficiency or stenosis in the course of rheumatic heart disease do considerably better than we have a right to expect they should. In particular the insufficiency relieves the lungs of congestion, and this patient had little or no evidence through this final illness, lasting four years, of either acute pulmonary edema or hemorrhage. A few patients have interatrial septal defects, likewise relieving the lungs somewhat, and they too get along better. In this case the description of the cervical veins and liver pulsation, helpful in recognizing tricuspid disease, is wanting.

I do not find enough evidence to assume that this patient had malignant disease anywhere in the body. I think I can account for the whole course by chronic rheumatic heart disease, but then what was the fatal factor here?

This patient, who was well treated for four years with low-sodium diet and mercurial diuretics twice a week, did remarkably well but finally failed in spite of the previously successful measures. The first clue to this impasse is that these patients fail to respond to mercurial diuretics as they previously did and finally do not respond at all; they become swollen and edematous, and on further study a lowered serum sodium and very often a low serum chloride are found. Associated with this is an increase in the nonprotein nitrogen. This situation, called by Schroeder[2] the low-salt syndrome, is very complicated. If it were a simple electrolyte imbalance, the administration of 200 cc. of 5 per cent hypertonic saline should be very beneficial. Sometimes it is, but often it is of only transient benefit.

Ordinarily with mercurial diuresis the augmented excretion of sodium carries with it its fluid complement and the circulation is adequate to present the kidneys with more blood plasma, fluid and electrolytes from the distant parts of the body. That is the favorable situation that usually obtains with mercurial diuretics. However, when other systems of the body, including the heart, become inadequate to present the kidneys with these electrolytes and fluid from the distant pools of edema in the body, then the mercurial diuretics fail to act and an impasse is reached. I believe that is the situation that existed in the end and is perhaps the reason that this patient who had responded so well for four years finally failed to respond and died. It is remarkable that we do not encounter this situation more often. Although temporary benefit may occur, relatively few of these patients can be brought back into balance for any appreciable length of time by juggling their electrolytes. It is a somewhat discouraging situation to deal with from a practical angle.

In conclusion, I believe this patient had chronic rheumatic heart disease with extensive scarring of the mitral valve with predominant regurgitation and possibly an element of stenosis. The cause of death was congestive failure and, probably, the therapeutic dilemma presented by the low-sodium syndrome.

Dr. Benjamin Castleman: Dr. Balboni, have you any comment?

Dr. Gerardo M. Balboni: I would like to congratulate the family physician who took care of this patient. She developed chorea at the age of ten and was taken care of by the same physician all those years.

Dr. Bland: May I say one word about chorea and rheumatic heart disease? Dr. T. Duckett Jones and I have been much interested in that for a long time. There is a special group of children who developed chorea without any other rheumatic stigmata or signs of concurrent infection — so-called pure chorea. At the time of their illness only 2 or 3 per cent showed cardiac involvement. Some physicians have even doubted that all of this "pure" chorea was of rheumatic origin. However, our follow-up studies[3] twenty years later reveal that almost one third of this group have now developed mitral stenosis — in many instances with no other signs of rheumatic activity in the interim.

Clinical Diagnoses

Rheumatic heart disease.
Congestive heart failure.
?Carcinoma of lung with metastasis.

Dr. Bland's Diagnoses

Rheumatic heart disease with mitral regurgitation and stenosis.
Giant left auricle.
Congestive failure.
"Low-salt" syndrome.

Anatomical Diagnoses

Rheumatic heart disease with marked stenosis of mitral and tricuspid valves.
Giant right auricle.
Congestive heart failure.
Anasarca.
Cardiac cirrhosis.
Senile osteoporosis with compression fracture of vertebras.

Pathological Discussion

Dr. Castleman: This patient had very severe peripheral edema, marked ascites — the abdomen contained a liter of fluid — and over a liter of fluid in the chest. This is a photograph of the heart

Figure 2.

with the vessels tied off as it appeared when filled with blood. The vessel at the top is the ascending aorta. The huge chamber to the left and below the aorta is almost all right auricle (Fig. 2). The cause of the enlarged right auricle was stenosis of the tricuspid valve, through which we could barely get one finger. The left auricle was large, but only about one fifth the size of the right auricle; there was also stenosis of the mitral valve of about the same degree as the tricuspid. The aortic valve showed only very slight interadherence of the cusps and there was no involvement of the pulmonary valve. The large x-ray shadow therefore is almost entirely the right auricle. We have seen a few cases of an enlarged right auricle that has produced the same elevation of the bronchus that we so often ascribe to an enlarged left auricle. The patient's long life was certainly due to the help that the stenosis and regurgitation of the tricuspid valve, as Dr. Bland said, gave in preventing congestion in the lungs. The tricuspid stenosis really produced most of her symptoms rather than the mitral stenosis. It is interesting that although the arterial tree in the lung showed atherosclerosis it was very mild; the lungs did not look like those of a patient with severe mitral stenosis. The liver showed a very mild but definite cardiac cirrhosis.

Dr. Bland: Don't you think the point to make about the elevation of the left bronchus is that ordinarily the left auricle goes back toward the right, sometimes actually to the right side? In this case it was not possible for the left auricle to extend to the right, so that perhaps moderate enlargement of the left auricle under these circumstances did push the bronchus up. Why did the patient die?

Dr. Castleman: I should think from heart failure. We were unable to see anything in the kidneys that would incriminate them; on the other hand, with the low salt syndrome, I do not think that we would find very much. We have not yet been able to find anything that we can put our fingers on in cases known to have a low-sodium syndrome.

A Physician: Were there any Aschoff bodies?

Dr. Castleman: There were some suspicious areas in the myocardium that may have been evidence of activity of the rheumatic state.

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CASE 38232

Presentation of Case

A sixty-two-year-old man was admitted to the hospital because of chronic cough.

Five months before admission, following a chest cold, the patient developed a chronic cough productive of a small amount of thin clear sputum that persisted in spite of treatment with many different medicines. The cough improved somewhat in the month before admission, except that he noted that when he was in the supine position he would develop a respiratory rattle that cleared with coughing. There had been no hemoptysis, night sweats, weight loss or known exposure to tuberculosis. Chest roentgenograms three months and two weeks before admission showed a lesion in the right lung; there was no change between the two examinations.

Physical examination revealed a thin man in no distress. There were a few small firm lymph nodes in the posterior triangles of the neck. The chest, heart, abdomen and extremities were negative. The prostate was diffusely enlarged to twice normal size; it was nontender and non-nodular.

The temperature was 98.4°F., the pulse 80 and the respirations 22. The blood pressure was 130 systolic, 70 diastolic.

The urine, of specific gravity 1.020, was normal. Examination of the blood showed a hemoglobin of 17.5 gm. and a white-cell count of 13,500. The non-

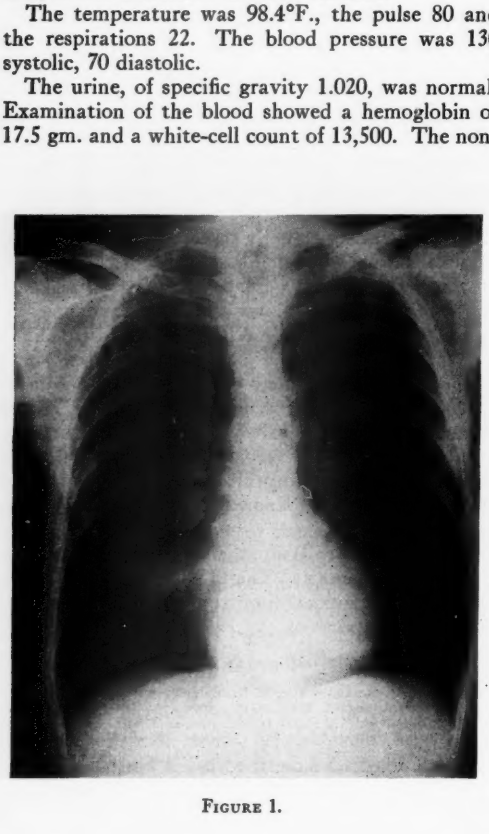

FIGURE 1.

protein nitrogen was 37 mg. and the total protein 6.8 gm. per 100 cc. Roentgenograms of the chest showed some emphysema; the right middle lobe was considerably reduced in size and contained a hazy, rather homogeneous density, which was especially dense in the lateral segment (Fig. 1). No definite mass could be made out at the right hilus and no enlarged mediastinal or hilar lymph nodes were seen. Comparison with the outside x-ray films showed no essential change. Grid films of the chest showed no definite abnormality of the bronchi. Bronchoscopic examination showed a normal upper trachea and a slightly widened, but mobile, carina. There was considerable inflammatory reaction on the right side and the middle-lobe orifice was concentrically narrowed to about one eighth of its normal size; there was much inflammation around this orifice, but the mucosa was normal in appearance and no tumor was seen. The orifice of the right-lower-lobe bronchus was also somewhat narrowed and inflamed; the apical and basal segmental bronchi were patent. The right-upper-lobe orifice and the left main bronchus and its branches were normal. Cytologic examinations of material removed at bronchoscopy and of sputum were negative for tumor cells. An electrocardiogram was normal.

On the eleventh day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. J. GORDON SCANNELL*: Before proceeding any further, since there is a paucity of clues in the protocol, may we see the x-ray films?

DR. STANLEY M. WYMAN: The earliest examination and the examination a month later were not done in this hospital. All three examinations show a process in the right middle lobe that is, as described in the protocol, hazy and homogeneous and is most marked in the lateral segment but also involves the medial somewhat (Fig. 1). The entire middle lobe, which is well shown on this view, is greatly reduced in size. The chest otherwise shows no active disease but there is considerable emphysema, manifested by the bulging of the sternum anteriorly. The bronchi are quite well seen in the posteroanterior grid film and are not unusual. There are no apparent enlarged lymph nodes in the hilar region or superior mediastinum.

DR. SCANNELL: Given the history of a sixty-two-year-old man with a change in his cough habits of five months' duration, absence of respiratory symptoms before that time, and these x-ray findings, I do not see how one can fail to make a tentative or working diagnosis of carcinoma of the lung. Having done that, the next logical step would be an exploratory thoracotomy. This does not mean the working diagnosis is the final diagnosis, but there is sufficient evidence to proceed.

Having decided that the diagnosis is "carcinoma until proved otherwise," then I am in a position to indulge in a few speculations. What are the alternative diagnoses and what clues in the protocol will support these diagnoses?

The first alternative diagnosis is tuberculosis. Although there is no statement in the protocol that acid-fast organisms were sought for, I assume that they were, either here or elsewhere, and were not found. In support of the diagnosis of tuberculosis — and by tuberculosis I mean a reasonably old and stable lesion — are one or two clues. This patient had bilateral small scattered lymph nodes in the posterior cervical triangle, which I suspect may have proved to be old acid-fast lymph nodes if subjected to biopsy. Secondly, the endoscopic appearance was consistent with tuberculous infection, especially in that this process was limited not merely to the middle lobe but to the basal segments of the lower lobe as well. It would be rather unusual with

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collapse not to see the tumor on bronchoscopy. Generally on bronchoscopy one can make the diagnosis of carcinoma in about 50 to 60 per cent of the patients if one fortifies that with cytologic examination of the sputum, but in a patient with this type of lesion the batting average on bronchoscopy should be considerably higher. This makes me think more of tuberculosis or some other inflammatory lesion. In favor of tuberculosis also is the failure of the process to change appreciably over the five months before admission; were it carcinoma, it is reasonable to expect some change in that period of observation. Against the diagnosis of tuberculosis are the failure to find the organisms, the age of the patient and the clinical history.

Could this have been a chronic pneumonitis, nonspecific in nature, possibly on the basis of an old collapsed middle lobe, which might have been traceable back to childhood diphtheria, pertussis or some other disease? It is possible that the patient had forgotten what diseases he had had. Though it may have been an old collapsed middle lobe, I am disinclined to that diagnosis because of the recent appearance of the symptoms, going back only five months; therefore, I think it is dangerous to assume it was an old process in the lung. I shall call your attention to the fact that this patient was not a patient in whom an incidental finding was made in the course of a chest-survey examination. He had had symptoms that brought him to a physician and led to multiple x-ray examinations. Although it could have been a chronic pneumonitis, I am reluctant to make that diagnosis in a patient who had a recent change of symptoms. The same argument is even more applicable to a diagnosis of atypical pneumonia — it is dangerous to make such a diagnosis in a sixty-two-year-old man with a relatively short history.

Another alternative diagnosis is benign tumor of the bronchus, such as an adenoma. Adenomas are usually central in nature and, when they cause a collapsed middle lobe, should be readily visibl by bronchoscopy. There should not be the extension of the change into the lower-lobe bronchus unless the latter was a response to a productive exudate from the middle lobe that was draining into the lower lobe this thin clear sputum that I am told about in the history. I think it is beyond likelihood that this represented a benign tumor.

Another tumor of the lung is alveolar adenomatosis, but this, almost by definition, is a peripheral lesion, not a lesion that manifests itself by collapse. This fact places the lesion at the segmental level. The lesions of alveolar adenomatosis are usually multicentric and not large. The only clue suggestive of that diagnosis was the thin, clear, possibly profuse sputum of which the patient complained. For the reasons given, in addition to the fact that cytologic smears of the sputum were negative, I shall rule that diagnosis out.

Lymphoma I might mention for the sake of covering all possible avenues of retreat, and similarly metastatic carcinoma with no primary tumor discoverable. I am inclined to disregard the prostatic finding.

I shall return to the working diagnosis of carcinoma of the lung, bronchogenic in nature, because I have been unable to establish a firm alternative diagnosis.

One comment on the management of this problem I should like to make is to remind you how frequently a biopsy of palpable cervical lymph nodes may be the basis for making a specific diagnosis upon which one can plan therapy. It is possible the operation on the eleventh day was a biopsy on the cervical lymph nodes. If it was not, the physicians in charge were presumably not impressed by the physical characteristics of the nodes in question. Another comment is that the patient had x-ray follow-ups over a period of three to five months. So long as it is intelligent, x-ray observation is justified and often valuable in suspicious lesions; when it becomes procrastination, it is dangerous.

Perhaps the patient may have had an old infarct in the lung, but as this alternative just occurred to me this minute, I shall not elaborate upon it.

A PHYSICIAN: I should like to ask Dr. Scannell if he places any significance on the hemoglobin of 17 gm.?

DR. SCANNELL: In a man who has a long-standing emphysema I imagine it is due to a secondary polycythemia.

DR. BENJAMIN CASTLEMAN: Dr. Soutter, would you tell us the opinion on the ward?

DR. LAMAR SOUTTER: I bronchoscoped this patient and later assisted the resident with the resection of the right middle lobe of the lung. At the time of bronchoscopy, there was about the right-middle-lobe orifice a good deal of inflammation. The diagnosis in our opinion lay between a carcinoma of the bronchus and a nonspecific inflammatory lesion of the parenchyma. The sputum studies were negative for tuberculosis. The constriction of the middle-lobe orifice was inflammatory in type; there was no hypertrophy of the type that is sometimes seen when there is a carcinoma in a bronchus beyond the view of the bronchoscope. That gave us sufficient evidence that we were dealing with an inflammatory process. Accordingly, we made a diagnosis preoperatively of chronic pneumonitis of the right middle lobe. Because of the patient's history and the tendency of chronic inflammation of the lung to cause acute exacerbations of infection, we felt that the middle lobe should be removed. When we observed the lung at the time of operation we were reasonably certain that the process was inflammatory and not malignant. There were well defined fissures between the lobes of the lung, so the removal of the middle one was relatively simple technically.

Clinical Diagnosis

Chronic pneumonitis.

Dr. Scannell's Diagnosis

?Carcinoma of the lung.

Anatomical Diagnosis

Lipoid pneumonia (*paraffinoma of lung*).

Pathological Discussion

Dr. Castleman: The middle lobe was small, half the size of a normal middle lobe, and along one aspect the pleura was very thick but apparently not adherent to the chest wall. The process was gray and involved a large area about the size that you see on the x-ray film. We also found two or three smaller lesions that measured up to 1 cm. in diameter that had exactly the same grayish-white fibrous appearance. Certainly the gross appearance was that of a non-neoplastic lesion, probably some form of inflammatory condition.

A section of one of these small nodules showed compensatory emphysema around the scar, indicating that the involved area of lung was probably three or four times its present size before the process developed. In another area the development of a secondary bronchiectasis was quite evident. In the scars were a lot of varying-sized empty spaces that were sudanophilic — the characteristic picture of lipoid pneumonia or paraffinoma of the lung. A resident, whom we immediately despatched to question the patient, found out that for the last five years the patient had been taking a tablespoonful of mineral oil every night for constipation. There is no question that this was the cause of these lesions. I wonder whether there were lesions in the other lung; paraffinomas usually occur bilaterally and in the dependent portions of the lungs. We were able to squeeze out some oil and occasionally one can pick up the oil in the sputum. It certainly is important in these so-called chronic pneumonitis cases to inquire whether the patients have been taking mineral oil, although I doubt whether the treatment would have been any different in this patient.

We were unable to find an occlusion of the bronchus, Dr. Soutter, unless the occluded part that you described was proximal to the resected edge.

Dr. Soutter: It was not occluded; it was more constricted than this bronchus normally is. It is worth while to mention that in a patient who has as much emphysema as this one did, with a limited pulmonary reserve, it would not have been safe to have done a pneumonectomy; had he had a carcinoma, we should have had to content ourselves with this degree of extirpative surgery or have run the serious risk of a postoperative fatality.

Dr. Castleman: If one or two small lesions were felt in the lower portion of the upper lobe or in the lower lobe, and if the middle lobe lesion was believed to be a carcinoma, it is possible that a pneumonectomy would be considered. The pathologist would be able to distinguish very easily with a frozen section at operation between carcinoma and paraffinoma.

Dr. Soutter: There was no question of how radical a procedure to do in this case because of the patient's limited pulmonary reserve. There was no abnormality that could be palpated in the other lobes. This does not, of course, completely exclude the presence of other disease.

Dr. Castleman: This type of lesion should be firm at this late stage. It may be soft in the early stages of lipoid pneumonia that you see in infants who have a diffuse inflammatory condition, but as the process becomes chronic, it scars and sometimes produces a dimpling in the pleura such as you often see in carcinoma.

Dr. Wyman, can you see any lesions in the other lung?

Dr. Wyman: I cannot see any more lesions. I am sure there must be small foci. I agree that it is unusual to see only one lesion, and the lower lobe is a more common location.

Dr. Scannell: Why is it that mineral oil, which is not a fat, becomes fat when it is in the lung?

Dr. Castleman: It is not a true fat; it takes the Scharlach R. Stain but not osmic acid. The better name is paraffinoma. In addition to the foreign-body reaction set up by the oil there may be more reaction because often the mineral oil contains other irritants to the lung, such as menthol, to make the oil more palatable.

A Physician: I had the opportunity to question this patient; he had not taken any mineral oil for five months before admission. He had also used nose drops.

Dr. Castleman: This was a chronic process that went back years.

Dr. Bland: What has happened to the cough?

Dr. Soutter: The patient was free of cough when he went home.

Dr. Alfred Kranes: Can you distinguish between this and the so-called cholesterol pneumonias?

Dr. Castleman: The cholesterol pneumonias are more diffuse and do not scar down as far as this; the fat is cholesterol and is in the phagocytes. It is not in large droplets as it was in this case.

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THE SOCIETY MEETS AGAIN

THE annual meeting of the Massachusetts Medical Society was held, as predicted, on May 19, 20, 21 and 22. The attendance at the meeting was 2701, and that of the Woman's Auxiliary was 150.

The usual succession of events took place. The Council met during the evening of May 19, the official annual meeting of the Society itself being held in the afternoon of the following day. The usual general sessions for the delivery of scientific papers occupied much of the three latter days of the convention, with the specialty sections meeting at luncheons on the same days. High lights of the gathering were the delivery of the Shattuck Lecture by Dr. Derek E. Denny-Brown on May 21 and the annual dinner on the same evening. The Shattuck Lecture has appeared in an earlier issue of the *Journal*.

At the annual meeting of the Society several interesting events took place. John Franklin Enders, Ph.D., eminent bacteriologist and chief of the research division on infants' diseases at the Boston Children's Hospital, was elected to associate membership; the fifty-year members received their tokens of esteem; and the three representative graduating students selected by the deans of the medical schools were presented with their rewards. In a forthright and forceful message on the "state of the Society" President Ohler summarized its achievements along the lines of postgraduate education and public relations and issued some sound advice concerning its attitude toward public-health activities. The meeting ended with the annual discourse, published in the May 22 issue of the *Journal*.

At the annual dinner John W. Cline, M.D., president of the American Medical Association, spoke eloquently of the achievement of the Association and its relations with its membership, the public and the Federal Government.

The meeting of the Woman's Auxiliary was held on May 20 and 21 at the Sheraton-Plaza Hotel, with Mrs. Harold J. Wahlquist, president of the National Auxiliary, as guest of honor. On this occasion Mrs. George E. McCabe of Worcester took office as president, Mrs. James M. Ward of Quincy succeeding her as president-elect.

The meeting of the Council on May 19, though prolonged, provided an opportunity for the ventilation of several controversial matters, as well as for the election and introduction of the new officers of the Society: Dr. Thomas H. Lanman of Boston, as president; Dr. Frederic Hagler of Springfield, as president-elect; Dr. John J. Curley of Leominster, as vice-president; and Dr. Sara M. Jordan of Boston, as orator.

Two recommendations of the Executive Committee's subcommittee on Blue Cross-Blue Shield Problems, acting with the Committee on Ethics and Discipline, were debated at length, as they had been at the meeting of the Executive Committee. The first of these was that

it is the sense of the Executive Committee that the Blue Shield should not be called upon to make payments for professional services rendered to service ward patients except where the participating physician actually rendering the service is entitled to receive and retain the compensation paid therefor, and that a statement of this action be referred to the Board of Directors of the Blue Shield.

The second recommendation was

that the Executive Committee recommend to the Council for its adoption the following principle: "That a member of the Massachusetts Medical Society should not accept or assign a fee for professional services from a third party when such a fee is not available for his own personal use."

Both recommendations were finally accepted by a large majority.

The report of the Subcommittee on Home Care of the Committee on Public Relations and the Committee on Medical Economics, acceptance of which as informational had been recommended, was tabled. Its tabling was the result of the confusion that still surrounds the subject and a general suspicion of it on the part of practitioners.

The report of the Committee on Public Health was accepted, after a long discussion, with an amendment that provided for further study of the Union Health Department Act, before the Council finally approved or disapproved it. The Committee's Subcommittee on Pilot Clinics, which had voted to endorse two more short-term screening clinics, in accordance with the action taken by the Council at the annual meeting in 1949, finally had its report accepted, after a lengthy debate, with an amendment making it informational only.

This meeting of the Council seemed to demonstrate the possibility that two inferences, at least, might be drawn: first, that the Council, with debate unlimited, continues to fulfill its manifest destiny as a democratic institution; secondly, that it is not availing itself of the purpose for which the Executive Committee was created, which is, by screening the reports of committees, to save the Council's time. If the councilors wish to have both the Council and the Executive Committee as functionally effective as possible, they should waive the more senatorial of their prerogatives and debate less extensively and more closely to the point.

ARTHRITIS AND RHEUMATISM

THE expenditures of the Arthritis and Rheumatism Foundation have risen in three short years from $19,000 through $115,000 to the impressive total of $177,000. This last sum of money has been apportioned about equally in six main channels — research, clinics, clinical facilities, fellowships, medical education and public information. As an account of its stewardship the Foundation has published a brochure, "The Start of a Conquest," which should give satisfaction to everyone who wonders just how much of his check reaches the objective and how much goes into overhead and campaign expenses. Although the actual figures within each category of expense are not listed (unfortunately), the implications of the graphs presented are that campaign expenditures have remained stable while the increased income has gone into the six activities listed above. As part of its public-information program, the Foundation is publishing a bulletin on rheumatic diseases as its official scientific publication, with nationwide distribution. This will be mailed to physicians on request.

In addition, an illustrated booklet on "Home Care in Rheumatoid Arthritis" has been prepared for the purpose of orienting the patient in details that contribute to his well-being and medical care — measures that the patient may use at home under the direction of his physician. The booklet is available to physicians only and may be obtained for ten cents a copy at 201 Devonshire Street, Boston 10, Massachusetts.

MILITARY AND CIVILIAN MEDICINE

A THREE-DAY military-civilian medical program of ambitious proportions will be presented June 23-25 at Murphy Army Hospital in Waltham. This symposium, primarily on military medicine, will be opened by Major General George E. Armstrong, Surgeon General of the Army. After the opening address twenty-three subjects vital to medical and surgical practice, both military and civilian, will be presented by doctors in uniform and discussed by doctors in mufti — the latter consisting mainly of prominent physicians and surgeons of the Boston area. In addition, a number of scientific and technical exhibits will be on display.

This largest military-civilian medical symposium yet to be held in New England is intended, — with an appreciation of the thesis that the armies of democracy are citizen armies, — to serve the practitioner in tweeds as well as the practitioner in khaki. Thus hyperparathyroidism is featured in the program as well as wound infections; arthritis and treatment of tuberculosis, as well as compound fractures due to battle injuries and combat psychiatry.

LEMUEL SHATTUCK AWARD

At the annual meeting of the Massachusetts Public Health Association, held in Boston on April 24, the third Lemuel Shattuck Award was conferred on Professor Curtis Morrison Hilliard, since 1914 head of the Department of Biology and Public Health at Simmons College.

In the presentation of the award by Professor Murray P. Horwood, Professor Hilliard's activities in the Red Cross, the Massachusetts Tuberculosis and Health League, the National Tuberculosis Association, the Massachusetts Civic League and the Massachusetts Public Health Association were listed as coming from one who is "an example of what a high-minded citizen and public servant should be."

The previous two presentations of the award, established by the Massachusetts Public Health Association in 1950 to honor a resident of New England for achieving outstanding distinction in the field of public health, were to Dr. C.-E. A. Winslow and Dr. Henry D. Chadwick.

Professor Hilliard well merits the distinction of being the third recipient of this award, for which no lack of suitable candidates in the years to come is anticipated.

Philadelphia Medical and Surgical Journal. — This is to be a bimonthly — a neat, respectable sheet, with evidences enough in the first number to show that men of thought are the conductors. . . . May the enterprise thrive, and the projector get something more substantial than praise in exchange for literary drudgery. The printer should spell correctly, hereafter, the name of the city in which he resides.

Boston M. & S. J., *June 9, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Barrett — Edward W. Barrett, M.D., of Medford, died on May 17. He was in his eighty-third year.

Dr. Barrett received his degree from Jefferson Medical College of Philadelphia in 1902.

Stansfield — Clarence W. Stansfield, M.D., of Fall River, died on May 17. He was in his seventy-second year.

Dr. Stansfield received his degree from the University of Maryland School of Medicine in 1906. He was a fellow of the American Medical Association.

He is survived by his widow and two daughters.

NONCLINICAL NOTES

Dr. Charles-Edward Amory Winslow, professor-emeritus of public-health medicine at Yale University, has been awarded by the president of the World Health Organization at Geneva the Leon Bernard Foundation Medal and Prize for outstanding contributions to social medicine.

BOOK REVIEWS

A Textbook of Medical Conditions for Physiotherapists. By Joan E. Cash, B.A., M.C.S.P. (Teachers' Certificates). With a foreword by Frank D. Howitt, M.D. 8°, cloth, 350 pp., with 12 illustrations and 11 plates. Philadelphia: J. B. Lippincott Company, 1951. $5.00.

There are many books on the armamentarium and the technics of physiotherapy, but few of them get behind this display of means and attempt to explain why or give the reasons for physiotherapy. In a therapeutic medium so recently advanced to honorable standing in medical practice, this is not an easy task. This book was written by a teacher of physiotherapy for physiotherapists to acquaint them with the medical conditions that are treated by physical measures and the reasons for such treatment. There is a general survey of the pathologic changes following injury and the process of repair. Diseases in the various anatomic systems that are benefited by physiotherapeutic measures are discussed in simple, nontechnical language. The book does not go into detail but provides a preliminary working knowledge of the various diseases. The chapters on diseases of the joints are particularly well done. The format of the book is good. There are a few good illustrations and diagrams; the book would be helped by more of these. There are a number of statements that need modification or correction, such as: "Acute bacterial endocarditis is rare and invariably fatal" and "It is doubtful whether the condition of visceroptosis really exists." The book is a valuable addition to the literature of physiotherapy and should prove most helpful both to those who practice and to those who prescribe physiotherapy.

John G. Kuhns, M.D.

Understanding Your Son's Adolescence. By J. Roswell Gallagher, M.D. 8°, cloth, 212 pp. Boston: Little, Brown and Company, 1951. $3.00.

This book is primarily directed toward the parents of adolescent boys, but the principles in it can be applied with only minor changes to girls, so it is really of great value to all parents of young children. Written as it is by a physician of wide experience with youngsters, and with much sympathy and understanding of psychiatry, it manages to convey a

great amount of mental hygiene without the handicap of professional jargon. If the lessons plainly stated in this book could be understood and adopted by parents, there would probably be less need for psychiatric treatment subsequent to adolescence.

The attitude of the author is consistently one of prevention but not of a sterile, punitive, depriving kind. His kind of prevention is the healthy, dynamic, vigorous variety. The youngster can learn to be responsible and enthusiastic only if his parents give him responsibility and act responsibly themselves, always with a realistic attitude toward the problems involved.

The book includes an excellent discussion of health facts for adolescents, a discussion of attitudes toward sex, some of the common causes of temporary failure in school, reading and speaking difficulties and the meaning behind some of the common forms of behavior.

It can be recommended with confidence to all parents, teachers and physicians.

DANA L. FARNSWORTH, M.D.

Diabetes Control. By Edward L. Bortz, M.D. 12°, cloth, 264 pp., with 16 illustrations. Philadelphia: Lea & Febiger, 1951. $3.50.

The name of this manual proves that the author grasps the crux of the diabetes situation today. It presents in simple, readable, nonpedantic language a helpful guide to diabetics. Humor and a broad humanitarian purpose, along with encouraging reviews of the recent discoveries in our knowledge of diabetes, are included, together with a hint for the furtherance of research. There are good stories and quotations to help the young and particularly the old. Complications receive attention and are sensibly discussed, with emphasis on prevention. Useful methods for teaching about diabetes are adopted from other manuals. Perhaps the seven pages devoted to the composition and food values of alcoholic beverages (out of a total of 264 pages)are a bit out of proportion, but this can be forgiven because the writer saves space by not mentioning for the patient the employment of potassium in coma.

ELLIOTT P. JOSLIN, M.D.

Heart Disease: Its diagnosis and treatment. By Emanuel Goldberger, M.D. 8°, cloth, 651 pp., with 229 illustrations. Philadelphia: Lea & Febiger, 1951. $10.00.

Dr. Goldberger is well known to cardiologists for his fundamental work in electrocardiography and for the two editions of his book, *Unipolar Lead Electrocardiography.* This volume is a concise exposition of clinical cardiology; its emphasis is not on electrocardiography. The book is divided into five sections: the normal heart, the abnormal heart, cardiac syndromes, systematic description of cardiac abnormalities and special conditions complicating heart disease. The newer methods of diagnosis are discussed at a length consistent with the conciseness of the text. X-ray examination is well covered; the illustrations are chiefly diagrams. Electrocardiography, as such, is covered in eighteen pages. The clinical discussions are clear and practical, and where the text is necessarily abbreviated the excellent bibliography will be found of value. Therapeutic recommendations are conservative, but there are some of interest, such as the intranasal use of mecholyl. Little drug therapy is suggested for hypertension, and none of the newer drugs, such as the veratrum alkaloids, are mentioned. Perhaps the author is correct, but a trifle conservative, when he says: "Surgical attempts to cure mitral stenosis by valvulectomy must still be considered experimental."

This is a good book for any physician to have as a ready reference.

HOWARD B. SPRAGUE, M.D.

The United States Public Health Service, 1798–1950. By Ralph C. Williams, M.D., Assistant Surgeon General, United States Public Health Service, Washington, D. C. 4°, cloth, 890 pp., with 192 illustrations. Washington, D. C.: Commissioned Officers Association of the United States Public Health Service, 1951. $7.50.

Dr. Williams relates the interesting history of the Public Health Service of the United States, beginning with the establishment by the fifth Congress of the Marine Hospital Service, approved by President John Adams on July 16, 1798. The material is divided into the major activities of the Service.

The first category deals with hospitals; it is noted that in 1799 Dr. Thomas Welsh became the first medical officer to be appointed to the Marine Hospital Service at the temporary hospital on Castle Island in Boston Harbor. In 1802 Dr. Charles Jarvis was appointed to succeed Dr. Welsh. The new hospital was erected in Charlestown and occupied in January, 1804. In 1870, the administration of the marine hospitals was centralized in the Treasury Department. The following chapters are concerned with quarantine (beginning in 1794) and the evolution of public health, noting that the first state health department was established in Massachusetts in 1869 and describing the work against bubonic plague, hookworm disease and the inauguration of the child-health program. The laboratory-research program began in a small way with a single-room establishment on Staten Island in 1887 and has expanded into the present-day National Institutes of Health, with its seven separate institutes. The section on field studies and demonstrations relates the story of yellow fever and Dr. Walter Reed and his associates, the work of the Puerto Rico Anemia Commission, plague control, pellagra, trachoma, malaria and mosquito control, the extensive stream-pollution campaign, drug addiction, mental hygiene, the communicable-disease center and other programs. There are sections on intragovernmental and international health relations. The sections on "Leadership and Leaders," "Those Who Carry On" and "When War Comes" are of a historical character and include the activities of the Service in World War I. There are large chapters on World War II and on public health in the mid-twentieth century. There is a comprehensive index, and the book is profusely illustrated with portraits and pictures of institutions and reproductions of documents. The price is low for such a publication. The book is recommended for all medical and public libraries.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Amenorrhea. By Lawrence M. Randall, M.D., section on obstetrics and gynecology, Mayo Clinic, and Thomas W. McElin, M.D., fellow in obstetrics and gynecology, Mayo Foundation, Rochester, Minnesota. 8°, cloth, 74 pp. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 109, American Lecture Series.)

This monograph is devoted principally to treatment. There are chapters on the literature of the subject, on war amenorrhea and on the Russian investigations made in 1945. There is a bibliography of 149 items. The subject has been thoroughly covered. (The 6 Russian articles were published in *Akush. i ginek.* 1:24-48, 1945. This periodical is in the Boston Medical Library.)

The Scottish Chemist's Index of Modern Remedies, 1951. First North American edition. Published by The Scottish Chemist, Glasgow, S.1, Scotland. 8°, paper, 116 pp. 1951. Distributed from Box No. 275, Terminal "A," Toronto, Ontario, Canada. $2.00.

This reference work is somewhat akin to the *New and Nonofficial Remedies of the American Medical Association.* The text is divided into two parts, the first for North America, the second for Great Britain. The material is arranged by therapeutic classes. There are comprehensive indexes of both sections.

Zahnärztliche Probleme in der Kinderheilkunde. By Dr. Med. et Med. Dent. F. Perabo. 8°, cloth, 119 pp., with 121 illustrations. Basel: Benno Schwabe and Company, 1951.

This monograph on dental problems in childhood discusses the development, anatomy and diseases of the teeth; the inflammatory diseases of the mucous membrane of the mouth; dislocations and fractures of the jaw; and anomalies. There is a good index, and the printing is well done, with excellent type.

Simplified Nursing. By Florence Dakin, R.N., and Ella M. Thompson, R.N. Fifth edition. 8°, cloth, 730 pp., with 78 illustrations. Philadelphia: J. B. Lippincott Company, 1951. $4.00.

This standard textbook on nursing was written for the student of practical nursing; the fifth edition has been completely rewritten. Much new material has been added and the text brought up to date. Lists of standard reference books and of national organizations distributing health information are appended to the text. There is also a glossary of medical terms and a good index. The book is well printed and should prove useful to those interested in practical nursing.

Progress in Neurology and Psychiatry: An annual review. Volume VI. Edited by E. A. Spiegel, M.D., professor and head, department of experimental neurology, Temple University School of Medicine. 8°, cloth, 562 pp. New York: Grune and Stratton, 1951. $10.00.

This new volume in a standard series covers the recent literature of neurology and psychiatry, including the basic sciences of anatomy, physiology and pharmacology. There is a special section on neurosurgery. The whole field of psychiatry is reviewed, including shock therapy, group psychotherapy, nursing and rehabilitation. There is a good index and the series should be in all medical libraries.

Obstetrical Practice. By Alfred C. Beck, M.D., consultant in obstetrics and gynecology, Long Island College Hospital and Norwegian Hospital, Brooklyn, New York, United States Naval Hospital, St. Albans, New York, and Vassar Brothers Hospital and St. Francis Hospital, Poughkeepsie, New York. Fifth edition. 4°, cloth, 1073 pp., with 969 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $10.00.

The first edition of this textbook was first issued in 1935. Since then, six editions or reprints have been published, including one each in Portuguese and Spanish. The fifth edition has been thoroughly revised and most of the text rewritten. One hundred and six new illustrations and an appendix of 22 reproductions of x-ray films have been added to this edition; 309 illustrations have been deleted. Lists of references have been appended to the various chapters, and there is a comprehensive index. The book is well published and should be in all collections on obstetrics.

Arzneitherapie der Herzkrankheiten. By Hans-Jürgen Oettel, Dozent für innere Medizin, Ärztlicher, Direktor und Chefarzt der inneren Abteilung des Wenckebach-Krankenhauses, Berlin-Tempelhof — Städtisches Krankenhaus Berlin-Tempelhof. 8°, cloth, 253 pp., with 15 illustrations. Stuttgart: Georg Thieme, 1951. Ganzleinen DM 27. Distributed by Grune and Stratton, Incorporated, New York.

This new monograph on the drug treatment of heart disease is written in a comprehensive style. There is a detailed list of contents, but unfortunately the lack of an index deprives the book of much of its reference value. The publishing is excellent, and the book should be in all collections on cardiology.

Maternal Nutrition and Child Health: An interpretative review. Kirsten U. Toverud, Genevieve Stearns and Icie G. Macy. Prepared for The Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council. 4°, paper, 174 pp., with 19 tables. Washington, D. C.: The National Research Council, National Academy of Sciences, 1950. $2.00. (Bulletin of the National Research Council, No. 123, November 1950.)

This monograph reports the results of a comprehensive worldwide survey of the nutrition of the mother in relation to the health and vigor of the infant at all stages of development. The material is divided into three principal categories: Maternal and infant mortality; specific nutritional factors; and maternal, prenatal and postnatal care. In Part 2, the various pertinent vitamins, iodine and milk, are discussed. A comprehensive bibliography of over 1000 titles concludes the text. Unfortunately, an index has not been provided. The monograph should be in all collections on the subject.

The Medical Works of Hippocrates: A new translation from the original Greek made especially for English readers. By John Chadwick, M.A. (Cantab.), and W. N. Mann, M.D. (Lond.), F.R.C.P., assistant physician to Guy's Hospital. 8°, cloth, 301 pp., with frontispiece. Springfield, Illinois: Charles C Thomas, 1951. $5.50.

This new translation of Hippocrates is designed especially for persons not familiar with the Greek language. The comprehensive translation of Littré is now practically unattainable; likewise, the translation of Francis Adams is uncommon. The printing is well done and there is a good index. The book should be in all collections on medical history.

An Atlas of Normal Radiographic Anatomy. By Isadore Meschan, M.D., professor and head of the Department of Radiology, University of Arkansas School of Medicine. With the assistance of R. M. F. Farrer-Meschan, M.B., B.S. (Melbourne). 8°, cloth, 593 pp., with 1044 illustrations. Philadelphia: W. B. Saunders Company, 1951. $15.00.

This new atlas of normal anatomy, written from a radiographic point of view, should prove valuable to radiologists, anatomists and physicians in general. The material is arranged according to the various systems of the body. Lists of selected references are appended to the various chapters and there is a good index. The publishing is excellent and the book is recommended for all medical libraries and to radiologists.

Comparative Physiology of the Thyroid and Parathyroid Glands. By Walter Fleischmann, M.D., Ph.D., Veterans Administration Hospital, Fort Howard, Maryland, and instructor in pediatrics, Johns Hopkins University School of Medicine, Baltimore. 8°, cloth, 78 pp. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 118, American Lecture Series.)

In this lecture the author discusses the thyroid function of fish, amphibia, reptiles, birds and mammals. Naturally, more than half the text is devoted to the mammals because of the large amount of work that has been done on this class of animals. An extensive bibliography is appended to the text. A list of the authors cited would have added to the reference value of the monograph.

Surgical Measures in Hypertension. By Reginald H. Smithwick, M.D., professor of surgery and chairman of the Department of Surgery, Boston University School of Medicine, and surgeon-in-chief, Massachusetts Memorial Hospitals, Boston. 8°, cloth, 95 pp., with 37 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $3.00. (Publication Number 61, American Lecture Series.)

This monograph is especially devoted to a discussion of the various types of splanchnicectomy by a recognized authority on the subject. A bibliography of 57 items is appended to the text.

Thyroid Function and Its Possible Role in Vascular Degeneration. By William B. Kountz, M.D., assistant professor of clinical services, Division of Gerontology, Washington University School of Medicine and the St. Louis City Infirmary Hospital, and consulting physician, Barnes Hospital and Lutheran Hospital, St. Louis, Missouri. 8°, cloth, 62 pp., with 8 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 108, American Lecture Series.)

This monograph chiefly discusses thyroid activity in relation to arteriosclerosis and the relation of this disease to disturbed metabolism. A short bibliography is appended to the text, and there is a good index.

Angiocardiography. By Charles T. Dotter, M.D., assistant professor of radiology, Cornell University Medical College, and assistant attending radiologist, New York Hospital, and Israel Steinberg, M.D., assistant clinical professor of radiology and medicine, Cornell University Medical College, assistant attending radiologist and physician to out-patients, New York Hospital, attending physician and chief of Chest Clinic, Sydenham Hospital, attending consultant in chest diseases, Veterans Administration Hospital, Bronx, and consultant in angiocardiography, U.S.N.H., St. Albans, New

York. 4°, cloth, 304 pp., with 635 illustrations. New York: Paul B. Hoeber, Inc., 1951. $16.00. (*Annals of Roentgenology, Volume XX.*)

This new volume in a well known series is devoted to the diseases of the circulatory system and the heart, and in addition discusses mediastinal and pulmonary tumors and pulmonary disease. A bibliography is appended to each chapter and there is a good index. The publishing is excellent in every way. It is interesting to note that the first 16 volumes of the *Annals* are now out of print. The atlas should be in all collections on radiography and on cardiac and pulmonary diseases.

Approved Laboratory Technic. By John A. Kolmer, M.D., D.P.H., Sc.D., professor of medicine and director of the Institute of Public Health and Preventive Medicine, Temple University; Earle H. Spaulding, Ph.D., professor of bacteriology, Temple University School of Medicine; and Howard W. Robinson, Ph.D., professor of physiological chemistry, Temple University School of Medicine. Fifth edition. 8°, cloth, 1180 pp., with 403 illustrations and 28 color plates. New York: Appleton-Century-Crofts, Incorporated, 1951. $12.00.

This standard reference book has been extensively revised and largely rewritten. Much new material has been added on a large number of methods, including phase microscopy, nomenclature of cells and diseases of the blood and blood-forming organs proposed by the Committee for the Clarification of Nomenclature, the rapid system for routine urinalysis by Waldman, Evans and Lasker, the Papanicolaou cytodiagnosis of cancer, the VDRL method for quantitative estimation of spinal-fluid protein, the *Rana-pipiens*-urine hormone test for pregnancy, Isenberg's method of staining spermatozoa, Alving and Miller's inulin clearance and the thymol-turbidity test for liver function and many other new methods. Eighteen collaborators assisted the authors in writing this new edition. An appendix contains valuable statistical material, including a table of four-place logarithms. There is a good index and the book is well published. It should be in all medical libraries and available to physicians interested in laboratory work.

A Textbook of Clinical Neurology. By J. M. Nielsen, M.D., clinical professor of neurology and psychiatry, University of Southern California, senior attending physician (neurology), Los Angeles General Hospital, and attending neurologist, Hospital of the Good Samaritan and Methodist Hospital, Los Angeles. Third edition, revised and reset. 4°, cloth, 709 pp., with 212 illustrations. New York: Paul B. Hoeber, Incorporated, 1951. $10.00.

The previous edition of this standard reference work was published in 1946. This new edition has been revised to bring the subject matter up to date. New chapters have been added on multiple sclerosis and on the psychoneuroses. The chapters on epilepsy, poliomyelitis and syphilis of the nervous system have been rewritten. The chapter on electroencephalography has been extensively revised and the subject of electromyography has been added. Lists of references have been appended to the various chapters, and there is an extensive index. The book should be in all medical libraries and available to all neurologists.

Epileptic Seizure Patterns: A study of the localizing value of initial phenomena in focal cortical sizures. By Wilder Penfield, C.M.G., M.D., D.Sc., F.R.C.S., F.R.S., professor of neurology and neurosurgery, McGill University, and director, Montreal Neurological Institute, and Kristian Kristiansen, M.D., assistant surgeon in charge of neurosurgery, Oslo City Hospital, Oslo, Norway. 8°, cloth, 112 pp., with 18 illustrations and 9 tables. Springfield, Illinois: Charles C Thomas, 1951. $3.00.

This monograph is based on the study of the localization of the initial epileptic discharge of 222 cases treated at the Montreal General Hospital. The main body of the text, devoted to seizure patterns, discusses initial unconsciousness; motor, sensory and autonomic motor and sensory phenomena; and psychic and miscellaneous phenomena. A short bibliography is appended to the text, and there is a good index. The monograph should be in all collections on epilepsy.

Diagnostische und therapeutische Technik beim Kinde: Eine Zusammenstellung Pädiatrischer Methoden für den Arzt des Kindes. By Dr. Med. Kurt Nitsch, Chefarzt der Kinderheilanstalt Bad Orb, Priv.-doz. für Kinderheilkunde an der Universität Göttingen. 8°, paper, 168 pp., with 26 illustrations. Stuttgart: Georg Thieme, 1951. Kartoniert DM 14.70. Distributed by Grune and Stratton, Incorporated, New York.

This monograph is devoted to diagnostic and therapeutic technic in children. The first three chapters discuss the subject in general, followed by physical therapy, the blood and the blood vessels, injection, infusion and transfusion. The following chapters deal with the special organs and the various systems of the body. The text is written in simple German and the material is well arranged. There is a good index. The manual should prove interesting to German-reading physicians.

Die generalisierten Tuberkulosen. By Dr. Med. F. Schmid. 8°, paper, 230 pp., with 60 illustrations. Stuttgart: George Thieme, 1951. Kartoniert DM 24.– (Tuberkulose-Bücherei). Distributed by Grune and Stratton, Incorporated, New York.

This monogaph is devoted to generalized and miliary tuberculosis. The progress of the disease is discussed, and there is a special section on granulomatosis benigna. A bibliography of 16 pages is appended to the text, and there is a good index. The monograph should be in all collections on tuberculosis.

The Effect of Hormones Upon the Testis and Accessory Sex Organs. By Norris J. Heckel, M.D., clinical professor of urology, Department of Surgery, University of Illinois College of Medicine; chairman, Department of Urology, Presbyterian Hospital; attending urologist, Ravenswood Hospital and Henrotin Hospital; and consulting urologist, Chicago Intensive Treatment Center, Chicago. 8°, cloth, 73 pp., with 21 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication Number 110. American Lecture Series.)

This monograph is devoted especially to a discussion of the common disorders of the male reproductive organs. An introduction deals with anatomy and physiology and is followed by chapters on the hormonal groups influencing the male organs and on the classification of male gonadal dysfunctions. There is a short bibliography and an excellent index.

Surgery of the Stomach and Duodenum. By Claude E. Welch, M.D., associate visiting surgeon, Massachusetts General Hospital, and clinical associate in surgery, Harvard Medical School. 8°, cloth, 349 pp., with 79 plates. Chicago: The Year Book Publishers, Incorporated, 1951. $8.50.

This handbook of operative surgery is intended as a practical guide for young surgeons and intentionally does not cover the whole field of gastric surgery. The text is illustrated with a large number of diagrammatic plates. There is a bibliography and an index. The publishing is well done, and the book should prove a valuable reference work.

Roentgen Anatomy: Roentgen anatomia. By David Steel, M.D., St. John's Hospital and Evangelical Deaconess Hospital, Cleveland. F°, cloth, 54 pp., with 108 plates. Springfield, Illinois: Charles C Thomas, 1951. $8.00.

The text of this new atlas of 52 plates of normal anatomic bony structures is written in English and Spanish. It is intended as a guide for quick reference and should well fulfill its objective. The plates are excellent. The atlas is recommended to all anatomists, roentgenologists and medical libraries.

NOTICES

NEW ENGLAND ROENTGEN RAY SOCIETY

At the annual meeting of the New England Roentgen Ray Society held on May 16 the following officers were elected:

President: Dr. Douglas J. Roberts, Hartford, Connecticut; vice-president: Dr. William S. Altman, Quincy, Massachusetts; secretary: Dr. Stanley M. Wyman, Boston; and treasurer: Dr. Magnus I. Smedal, Boston.

(*Notices concluded on page xv*)